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INPADOC Record

Title: **KR9603605B1: PROCESS FOR PREPARING ORAL OMEPRAZOLE**

Country: **KR** Republic of Korea

Kind: **B1** Examined Patent Application, Second Publication; since 970930 Granted Patent

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[No Image](#)

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Application Number: **KR1992000017403**

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Priority Number(s): **Sept. 24, 1992 KR1992000017403**

Abstract:

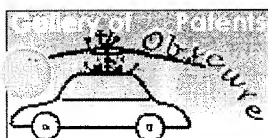
The composition for oral dosage containing omeprazole (I) is comprising hydroxypropyl beta-cyclodextrin (II) as soluble carrier, trometamin (III) or sodium hydroxide as alkalizing agent and moisture proof agent as 0.5-2, 0.5-2, 0.3-2 part to 1 part of (I). This formulation which has the characteristics as 95% dissolving within 1 minute consists of (1) dissolving (I) in ethanol, (2) dissolving (II) in water or ethanol, (3) dissolving (III) in water or ethanol, (4) mixing them and drying.



Family: **none**

Abstract Info: **DERABS C1999-139592 DERABS C1999-139592**

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(54) 경구용 오메프라졸 약제의 코어 조성물을 제조하는 방법

요약

내용 없음.

영세서

[발명의 명칭]

경구용 오메프라졸 약제의 코어 조성물을 제조하는 방법

[발명의 상세한 설명]

본 발명은 경구용 오메프라졸(omeprazole) 약제의 코어 조성물을 제조하는 방법에 관한 것으로서, 더욱 상세하게는 난용성인 오메프라졸의 용출성과 안정성을 향상시킴으로써 경구용 장용성 약제의 코어 조성물로 유용하게 사용할 수 있도록 경구용 오메프라졸 코어 조성물을 제조하는 방법에 관한 것이다.

최근 H₂-K⁺ ATPase 억제효과로 위산분비를 강력히 억제할 수 있는 오메프라졸 및 그 염 또는 기타의 벤조이미다졸 유도체들이 소화성 궤양치료에 응용되고 있으며, 이들 화합물들은 강력하고 지속적인 위산분비 억제효과를 가지고 있어서 기존의 H₂ 수용체 차단제를 대신하는 새로운 소화성 궤양치료제로 각광받고 있다.

그러나, 이러한 벤조이미다졸 유도체들은 일반적으로 물에서의 용출성과 용해성이 매우 나쁘고, 수용액 및 용출상태에서 쉽게 변색을 일으키며 분해가 매우 빠르기 때문에 경구용 제제화가 매우 어렵다. 특히 오메프라졸은 물에 거의 녹지 않으며 산성 수용액중에서 매우 불안정하여 산촉매 반응으로 매우 빨리 분해되며 증성용액에서도 분해되기 쉽다.

또한 오메프라졸은 25℃의 조건에서, pH 4 이하에서의 반감기는 약 7분, pH 7에서의 반감기는 약 38시간, 반면에 알칼리 영역인 pH 10에서의 반감기는 약 85일로 산성이 강할수록 매우 불안정해지고, 알칼리성이 커질수록 분해가 지연되며 더우기 고체상태에서도 흡습에 의해 변색과 함께 알칼리화를 일으키는 특성을 가지고 있다.

한편, 대한민국 특허공개 제87-1005호에는 오메프라졸을 염염태로 제조하여 안정화시키는 방법이 기술되어 있고, 대한민국 특허공개 제87-9117호, 제87-9718호에는 알칼리성 물질을 첨가하여 오메프라졸을 안정화시키는 방법이 기술되어 있다.

또한, 대한민국 특허공개 제90-2010호에는 특정의 염기성 아미노산을 첨가하여 오메프라졸 약제의 코어 성분을 안정화시키는 방법이 제안되어 있다.

일반적으로 난용성약물의 용출이 흡수의 속도단계가 된다는 점에서 조성물로부터 주약의 용출성은 오메프라졸과 같이 물에 거의 녹지 않는 약물인 경우에는 이의 용출증대가 제제의 품질을 좌우하는 중요한 요소가 되고 있다.

이런 관점에서 볼때 상기의 기술들은 알칼리성 물질을 오메프라졸과 단순히 혼합하여 오메프라졸의 안정화를 도모한 것이므로, 안정화를 위하여 많은 양의 알칼리화제가 요구됨과 동시에 경구투여시 소장에서 신속히 용출되지 못하는 결점을 가지고 있다.

또한, 베타-시클로덱스트린을 이용한 오메프라졸의 안정화는 독일연방공화국 특허공개 OE342778A1에 제안되어 있으나, 그 제조방법은 장시간의 제조과정을 요구하며, 이 방법만으로는 제조과정중의 분해를 막을 수 없을 뿐만 아니라, 이 조성물만으로는 장기간의 보관시에 외계 수분의 흡습과 자체 함유수분의 존재로 변색 및 분해를 막을 수 없어서 안정한 오메프라졸제제를 얻을 수 없다.

이에 본 발명자들은 오메프라졸이 상기와 같이 종래 기술들에서 나타난 문제점들을 해소하고자 오랫동안 연구한 결과 알칼리화제와 수용성 담체중 이용한 3성분의 고체 분산체를 제조하면 신속히 오메프라졸을 용출시키면서 안정성도 증대된 경구용 장용성 오메프라졸 약제의 코어 조성물을 효과적으로 제조할 수 있다는 것을 알게되어 본 발명을 완성하게 되었다.

따라서, 본 발명은 오메프라졸 경구용 제제를 제조하는데 사용되는 코어 조성물에 있어서, 높은 안정성을 가지면서 소장에서 신속하게 용출될 수 있도록 개선된 새로운 형태의 경구용 오메프라졸 약제의 코어 조성물을 제공하는데 그 목적이 있다.

이하, 본 발명을 상세히 설명하면 다음과 같다.

본 발명은 오메프라졸을 유효성분으로 하고, 여기에 안정화 성분을 혼합시켜서 경구용 오메프라졸 약제의 코어 조성물을 제조함에 있어서, 유효성분인 오메프라졸에 안정화 성분으로서 베타-시클로덱스트린 또는 그 유도체와 트로메타인 또는 수산화나트륨중에서 선택된 알칼리 화합물을 첨가 혼합시켜서 고체 분산체로 제조함을 그 목적으로 한다.

이하 본 설명을 더욱 상세히 설명하면 다음과 같다.

본 발명은 오메프라졸의 안정화 성분으로 베타-시클로덱스트린 또는 그 유도체와 알칼리 화합물을 첨가하여 고체분산체를 제조하는 방법에 관한 것으로서, 오메프라졸을 정제수, 에탄올 또는 그 혼합용액 등의 용제에 녹이고, 역시 정제수 또는 에탄올 등에 녹인 알칼리화제 및 베타-시클로덱스트린 또는 그 유도체를 첨가하고 교반시킨 후 감압건조기, 분무건조기 또는 동결건조기 등으로 건조하여 3성분으로 균일한 고체 분산체를 얻는다.

이렇게 얻어진 고체분산체는 안정한 상태이긴 하지만 보관중 수분침투에 대한 경시보존 안정성을 향상시키기 위하여 방습제를 첨가하여 사용할 수 있다. 이때 방습제로는 산화마그네슘이나 탄산마그네슘을 단독으로 사용할 수 있으나 혼합사용할 수도 있다.

본 발명에 있어서 사용되는 베타-시클로덱스트린은 글루코스 7개가 환상으로 결합된 올리고당으로 경구 투여시 인체에 무해하며 환상의 소수성 공동내에 약물분자 또는 약물분자의 구조의 일부를 포접하여 난용성 약물의 용해성 및 생체내 이용

를 향상, 불안정한 약물의 안정화, 액상물질의 분체화, 자극성 및 냄새의 개선 등에 이용되고 있는 물질로서, 본 발명에 사용할 수 있는 베타-시클로덱스트린의 유도체로는 예컨대 하이드록시프로필 베타-시클로덱스트린이 사용될 수 있다. 본 발명에 따르면 베타-시클로덱스트린 또는 그 유도체의 그 첨가량은 오메프라졸 1몰에 대하여 0.5-2몰로 사용하는데, 첨가량이 0.5를 미만이면 오메프라졸의 용출증대와 충분한 안정화 효과를 얻는데에 문제가 있고 2몰을 초과하면 단위당 무게나 과립의 부피증대로 실제생산에 문제가 따른다.

또한 본 발명에 사용되는 알칼리 화합물은 트로메타민 또는 수산화나트륨이 사용되고 그 첨가량은 0.5-2몰 사용하는데, 그 첨가량이 0.5몰 미만이면 충분한 알칼리성을 띠지 못하므로 안정화 되지 못하여 반감기가 단축되며 2몰을 초과하면 강한 알칼리성으로 인하여 인체투여시 자극을 일으킬 우려가 있다.

본 발명에 있어 사용되는 방습제는 오메프라졸 코어 전체 조성물 1중량부에 대하여 0.3중량부 내지 2중량부를 첨가하는 것이 좋고, 그 사용량이 과다하면 과습제 또한 점제로의 형성성과 크기에 문제가 발생되며 너무 적으면 방습효과가 감소된다.

본 발명에서는 감압가열건조, 분무건조법에 의해 고체분산체 형태로 제조함으로써 열에 의한 오메프라졸의 분해를 방지하고, 제조후 장기간의 보존 및 유통과정중의 안정성 유지에도 기여할 수 있도록 수산화나트륨, 트로메타민 등의 알칼리화제를 함유하고 있어서 제조중이나 장기간의 보존중에도 안정하다. 이러한 오메프라졸 고체분산체는 베타-시클로덱스트린 및 그 유도체의 높은 친수성으로 인하여 습윤성이 크고 분산된 오메프라졸의 입자크기가 단분자 내지는 클로이드 크기로 물리적인 분쇄법으로는 달성할 수 없는 크기이기 때문에 표면적이 극대화되어 오메프라졸의 속용출성을 제공하는 특징이 있다.

즉, 종래의 분쇄법으로는 오메프라졸을 분쇄하는 경우 얻어지는 입자크기에는 한계가 있으며 미분화 될수록 발생하는 열에 의한 분해가능성과 부작, 응집성이 커져 분쇄효과가 감소하는 경향이 있다. 또 응집성이 커지면 오메프라졸의 습윤성과 분산성을 나쁘게 하여 용출률을 저하시킨다.

그러나 본 발명의 시클로덱스트린 고체분산체는 입자크기를 한계 입자크기로 감소시킴과 동시에 위장관액에서의 습윤성과 분산성을 높여 속용출성을 확보할 수 있다.

또한 첨가된 알칼리화합물이 기존의 방법과 같이 단순한 입자의 혼합이 아니라 단분자 내지는 클로이드상으로 분산되어 있어서 적은 양으로도 전체 고체분산체에 알칼리환경을 제공하여 종래보다 우수한 안정화를 효과적으로 이룩할 수 있다.

그리고 함유된 방습제로 인하여 외부환경에 의한 인습시에도 저항성이 높고 안정한 오메프라졸 조성물을 유지할 수 있다.

한편, 본 발명에서 안정화 성분으로 베타-시클로덱스트린만 사용하게 되면 제조과정중 및 보관중의 수분 및 열에 의한 영향으로 좋지 못하고, 또 알칼리 화합물만을 사용하게 되면 제조공기로부터 고체분산체의 수득이 어렵고 알칼리화제로 인하여 조해, 인습의 염려가 있어서 좋지 못하다.

따라서, 본 발명은 유효성분인 오메프라졸에 베타-시클로덱스트린 또는 그 유도체와 알칼리화제를 함께 사용하면 고체분산체 형태로 코어 조성물을 제조함으로써 위 두 성분이 상승작용을 일으켜서 기존의 어느 것보다도 안정하고 용출성이 높은 고체분산체를 얻을 수 있다.

위와 같이 본 발명의 방법으로 제조한 3성분계 고체분산체는 오메프라졸, 베타-시클로덱스트린 또는 그 유도체, 알칼리화제의 3성분이 단분자적 내지는 클로이드상으로 분산되어 있기 때문에 기존의 방법, 즉 안정화제로서 인산일수소나트륨 또는 염기성 아미노산 등을 첨가하여 제조한 것보다 안정도가 월등히 증가하였으며, 용출성도 크게 향상되어 소장출수가 빠르고 용수율이 커서 본 발명의 경구용 오메프라졸 코어 조성물은 소화성 궤양 치료제를 장용성제제로 널리 유용하게 사용할 수 있다.

이하, 본 발명을 실시예에 의거 상세히 설명하면 다음과 같으나, 본 발명이 실시예에 의해 한정되는 것은 아니다.

[참고예 1]

수용액을 베타-시클로덱스트린 또는 그 유도체에 의한 오메프라졸의 안정성 향상

베타-시클로덱스트린(이하, β -CD로 칭함) 및 그 유도체인 2-히드록시프로필-베타-시클로덱스트린(이하, HPCD로 칭함), 디메틸-베타-시클로덱스트린(이하 DMCD로 칭함)를 각각 pH 7.0 인산염 완충액을 써서 1×10^{-4} M 농도로 조제하고 각각 오메프라졸을 100 μ g/ml 농도로 첨가한 다음 37 $^{\circ}$ C에 보존하면서 안정화 효과를 시험하여 그 결과를 다음 표 1에 나타내었다. 오메프라졸의 잔존량은 경시적으로 측정하여 1차식에 따라 그 분해반감기($t_{50\%}$)와 저장수명($t_{90\%}$)을 구하였다.

[표 1]

베타-시클로덱스트린 유도체에 의한 오메프라졸의 안정화 효과

시클로덱스트린	$t_{50\%}$ (시간)	$t_{90\%}$ (시간)
비첨가	17.97	2.52
β -CD	21.47	3.25
DMCD	31.96	4.81
HPCD	23.81	3.61

* $t_{50\%}$: 오메프라졸 50%가 잔존하는 시간(50%가 분해되는 시간)

* $t_{90\%}$: 오메프라졸 90%가 잔존하는 시간(10%가 분해되는 시간)

표 1에서와 같이 소장 pH 근처에서 오메프라졸의 안정성이 β -CD, DMCD 및 HPCD의 첨가로 오메프로졸 단독인 경우와 비교하여 그 반감기가 각각 19.5%, 77.8% 및 32.5% 증가되었다. 이것은 오메프라졸이 소장에서 용출된 후 흡수되기 전까지 장 내에 체류하는 동안의 분해를 지연시킬 수 있음을 의미한다.

[참고예 2]

pH 7.0 인산염 완충액중에서의 β -CD 및 HPCD가 오메프라졸의 용해성에 미치는 영향을 시험하였다. 시험방법은 일정농도로 조제한 β -CD 및 HPCD 용액 1ml에 오메프라졸을 과량 첨가하고 37 $^{\circ}$ C의 항온진탕수욕장치에서 48시간동안 격렬하게 진탕시키고 1시간 정지시킨후 0.45 μ m 멤브레인필터로 여과한 액을 고속액체 크로마토그래피로 분석하여 용해된 오메프라졸의 양을 산출하여 그 결과를 다음 표 2에 나타내었다.

[표 2]

베타-시클로덱스트린류에 의한 오메프라졸의 용해도 변화(pH 7.0)

정기된 농도 ($\times 10^{-4}$ M)	오메프라졸의 용해도($\times 10^{-4}$ M)	
	β -CD	HPCD
0	0.296	0.296
4	0.333	0.533
8	0.489	0.573
12	0.613	0.695
16	0.586	0.769
20	0.559	0.925

본 실험에서는 DMCD가 산업적인 공급이 불가능하므로 제외하였다. 오메프라졸의 용해도는 베타-시클로덱스트린류의 첨가로 농도 의존적으로 증대되었으며 $1.2 \times 10^{-4} \text{M}$ 의 β -CD 및 HPCD 존재하에서는 오메프라졸의 용해도가 각각 약 206 및 233% 증대되었다.

이러한 결과는 오메프라졸이 베타-시클로덱스트린류와 수용성 복합체를 형성한다는 것을 뒷받침하며 난용성인 오메프라졸에 대한 가용화 효과가 있음을 의미한다.

[참고예 3]

pH 10.0 완충액 완충액중 β -CD 및 HPCD가 오메프라졸의 용해성에 미치는 영향을 검토하였다. 시험방법은 참고예 2와 동일한 방법으로 하여 그 결과를 다음 표 3에 나타내었다.

[표 3]

베타-시클로덱스트린류에 의한 오메프라졸의 용해도 변화 (pH 10.0)

첨가된 농도 ($\times 10^{-4} \text{M}$)	오메프라졸의 용해도 ($\times 10^{-4} \text{M}$)	
	β -CD	HPCD
0	10.09	10.09
4	10.73	10.46
8	11.77	12.45
12	12.26	12.97
16	13.52	13.16
20	14.06	13.35

pH 10에서도 베타-시클로덱스트린류에 의해 오메프라졸의 용해성이 상기 표 3에서와 같이 증가하였으며, $1.2 \times 10^{-4} \text{M}$ 의 β -CD 및 HPCD의 존재로 오메프라졸의 용해도를 각각 2.15% 및 28.5% 향상시켰다.

이러한 결과는 오메프라졸의 해리가 증대된 알칼리영역에서도 오메프라졸과 시클로덱스트린류가 상호작용을 나타냄을 뒷받침한다. 이는 또한 알칼리매질에서도 고체분산체의 제조시 오메프라졸이 단분자적으로 분사됨을 의미한다.

[참고예 4]

pH에 따른 오메프라졸의 용해성 변화

여러 pH 용액중 오메프라졸의 용해성을 시험하였다. 시험방법은 각 pH 완충액에 오메프라졸을 과량 첨가하고 참고예 2와 같은 방법으로 시험하여 그 시험결과를 다음 표 4에 나타내었다.

[표 4]

pH에 따른 오메프라졸의 용해성

pH	오메프라졸의 용해성	
	$\mu\text{E/ml}$	용농도($\times 10^{-3}$)
7.0	102.9	0.2980
8.4	222.7	0.6446
9.0	321.6	2.3764
10.0	2,455.3	10.0900
11.0	1,727.4	5.0080
12.0	13,137.8	33.0341

오메프라졸의 용해성이 알칼리영역에서 크게 증가하여 특히 pH 12에서의 용해도가 큼을 알 수 있다.

[실시예 1~4]

오메프라졸과 β -CD 및 그 유도체인 HPCD의 2성분 고체분산체와 알칼리 화합물을 첨가한 3성분계 고체분산체를 다음 표 5의 조성으로 제조하되 각 성분을 사용용매에 완전히 용해한 후 40°C의 회전식 감압건조기에서 건조하고, 과량의 건조물을 분쇄하고 실리카겔 데시케이터에서 1일 건조하여 제조하였다.

[표 5]

고체 분산체의 조성

성분	실시예 1	실시예 2	실시예 3	실시예 4
오메프라졸	100mg	100mg	100mg	100mg
수산화나트륨	11.6mg	11.6mg	-	-
모노메타민	-	-	35mg	35mg
β -CD	323mg	-	323mg	-
HPCD	-	376mg	-	376mg
사용용매	역산용 정제수	이탄용 정제수	이탄용 정제수	이탄용

[비교예 1~5]

오메프라졸의 안정화에 미치는 알칼리화제의 영향을 검토하기 위하여 오메프라졸과 알칼리화제와의 건고물, 단순 물리적 혼합물 및 오메프라졸만의 건고물을 다음 표 5의 조성으로 하여 상기 실시예 1과 같은 방법으로 제조하였다.

또, 종래기술에서 안정화제로 사용한 인산일수소나트륨과 오메프라졸을 80mesh 이하로 분쇄하고 1 : 1 중량비로 혼합하여 비교예 5의 건고물을 제조하였다.

[표 6]

건고물의 조성

성분	비교예 1	비교예 2	비교예 3	비교예 4	비교예 5
오메프라졸	100mg	100mg	100mg	100mg	100mg
수산화나트륨	11.6mg	-	-	-	-
트로메타민	-	35mg	-	-	-
말산일수소나트륨	-	에탄올	-	-	100mg
사용용액	에탄올 정제수	-	에탄올 정제수	에탄올	-

비교예 6, 7

[비교예 6~7]

오메프라졸과 β -CD 또는 HPCD의 2성분 고체분산체를 다음 표 7의 조성으로 하여 제조하였다.

[표 7]

2성분 고체분산체의 조성

성분	비교예 6	비교예 7
오메프라졸	100mg	100mg
β -CD	329mg	-
HPCD	-	376mg
사용용액	에탄올 정제수	에탄올

[실험예 1]

상기 실시예 1~4와 비교예 1~7의 제제물들에 대하여 40℃~75% RH 조건에 개방상태로 보존하면서 3주간 경시변화시험을 하였고, 그 결과는 다음 표 8과 같으며, 3성분계 고체분산체가 안정함을 알 수 있다.

[표 8]

제제물의 40℃~75% RH에서의 변색 시험결과

제제물		변 색 도			
		초기	1주	2주	3주
전 고 물	비교예 1	B	C	C	C
	비교예 2	C	D	D	D
	비교예 3	C	E	E	E
	비교예 4	E	E	E	E
	비교예 5	B	E	C	D
고 체 분 산 제	비교예 6	C	C	C	C
	비교예 7	C	D	D	D
실시예	실시예 1	A	A	A	A
	실시예 2	A	A	A	A
	실시예 3	A	A	A	A
	실시예 4	A	A	A	A

* A : 백색 또는 연한 노란색, B : 붉은 유백색, C : 유백색, D : 붉은 갈색, E : 갈색

[실험예 2]

상기 실시예 1과 2에서 제조된 고체분산체와 상기 비교예 1,2,3,5에서 제조된 건고물 및 비교예 6에서 제조된 고체분산체에 대하여 각각 80mesh체를 통과시키고 용출시험을 하였다. 용출시험 조건은 대한약전 일반시험법중 용출시험법에 따라 제2법(퍼들법)으로 실시하였고, 다만 시험용액은 대한약전 일반시험법중 분해시험법의 제2액(pH 6.8) 500ml를, 퍼들 회전수는 50rpm으로 하였다. 오메프라졸 20mg에 해당하는 양을 달아 용출시험기에 넣고 경시적으로 용출액을 취하여 0.45 μ m 멤브레인 필터로 여과하고 고속액체 크로마토그래피법으로 분석하여 용출률을 구하였으며, 그 결과는 다음 표 9와 같다.

시험한 고체분산체는 모두가 같은 방법으로 처리하는 약품을 단독으로 사용한 것보다 원저한 용출증대를 나타내었다. 또 약물과 β -CD와의 2성분계 고체분산체(비교예 6) 보다 말랄리가 함유된 3성분계 고체분산체(실시예 1 및 2)가 급속한 용출증대를 나타내었다.

[표 9]

제제물의 용출 시험결과

구 분	지계물	용 출 률(%)				
		1분	3분	5분	10분	20분
비교예 1	건고물	90.05	92.33	97.00	97.05	97.80
비교예 2	건고물	20.08	35.26	44.50	53.77	67.47
비교예 3	건고물	7.55	7.58	10.80	19.01	32.05
비교예 4	건고물	9.56	17.55	26.75	45.80	62.43
비교예 5	고체분산체	46.53	62.35	69.52	73.84	90.10
실시예 1	고체분산체	94.23	97.85	99.04	99.32	99.75
실시예 2	고체분산체	96.75	99.05	99.21	99.89	99.78

* 용출결과는 백전률(%)

따라서, 실시예의 경우 상기의 표 8과 9에서 확인되는 바와같이 안정성이나 용출률의 면에서 비교예에 비하여 월등히 우수함을 알 수 있다.

[제조예 1]

오메프라졸- β -CD-트로메타민 고체분산체 및 물리적 혼합물의 제조

오메프라졸 100mg, β -CD 329mg를 달아 약물은 에탄올 10ml에 녹이고, β -CD는 정제수 15ml에 가운하여 녹이고 양자료를 혼합한 후 트로메타민 35mg을 정제수 5ml에 녹여서 혼합하였다. 이 혼합용액을 회전식 감압건조기를 써서 종발건고하였다. 과량의 건고물을 분쇄하고 실리카겔 데시케이터에서 1일 방치하여 고체분산체를 얻었다(제제물 1).

오메프라졸 100mg, β -CD 657.17mg, 트로메타민 35mg을 가지고 상기의 방법으로 하여 고체분산체를 얻었다(제제물 2).

별도로 제제물 1과 동일한 양의 세가지 성분을 달아 잘 혼합하여 물리적 혼합물을 얻었다(제제물 3). 또한 제제물 2와 동일한 양의 세가지 성분을 달아 잘 혼합하여 물리적 혼합물을 얻었다(제제물 4).

[제조예 2]

오메프라졸-HPCD-트리메타민 고체분산체 및 물리적 혼합물의 제조

오메프라졸 70mg, HPCD 263.2mg을 달아 에탄올 또는 메탄올 20ml에 녹이고 트리메타민 25mg을 달아 함께 녹인 후 교반한다. 40℃에서 회전식 감압건조기를 써서 중발건고하고 잔류물을 분쇄하여 실리카겔 데시케이터에서 1일 방치하여 고체분산체를 얻었다(제제물 5).

오메프라졸 70mg, HPCD 567mg, 트리메타민 25mg을 가지고 상기의 방법으로 하여 고체분산체를 얻었다(제제물 6).

별도로 제제물 5와 동일한 양의 세가지 성분을 달아 잘 혼합하여 물리적 혼합물을 얻었다(제제물 7). 또한 제제물 6과 동일한 양의 세가지 성분을 달아 잘 혼합하여 물리적 혼합물을 얻었다(제제물 8).

[실험예 2]

상기 제조에 1과 2의 각 제제물의 대하여 40℃-75% RH 조건에 개발상태로 보존하면서 3주간 경시변화 시험을 행하였고, 그 결과는 다음 표 10과 같다.

[표 10]

제제물 1~8의 40℃-75% RH에서의 함량 변화

제제물	함량(%)	비고
1	98.22	
2	99.99	
3	98.06	
4	97.99	
5	99.83	오메프라졸 단독용 92.48%
6	98.85	
7	98.13	
8	98.01	

상기 표 10에서 보면 약물 단독이 현저한 함량저하를 나타낸 반면 고체분산체나 물리적 혼합물의 경우는 β -CD 또는 HPCD 모두 높은 잔존율을 보여 주었다.

그리고 제제물 2, 4, 6에 대하여 80mesh체를 통과시키고 상기 실험예 1의 용출시험과 동일한 방법으로 용출시험을 하였으며, 시험결과는 다음 표 11과 같다. 고체분산체가 약물 단독이나 물리적 혼합물보다 현저한 용출 증대효과를 나타내었다.

[표 11]

제제물의 용출시험

용출시간	제제물 2	제제물 4	제제물 6	오메프라졸
1분	89.16	54.48	90.02	-
3분	89.99	68.07	93.85	-
5분	95.29	79.02	97.90	10.81
10분	98.49	88.37	98.00	19.01
20분	99.56	90.41	99.65	31.91

* - : 정량하지 않음 * 용출결과는 백분율(%)

[제조예 3]

오메프라졸-β-CD-수산화나트륨 고체분산체 및 물리적 혼합물의 제조

다음 표 12의 처방으로 제조예 1의 방법에 따라 알칼리화제로 수산화나트륨을 사용하여 고체분산체 및 물리적 혼합물을 제조하였다.

[표 12]

제제물의 조성

성분(mg)	고체분산체				물리적 혼합물			
	1	2	3	4	5	6	7	8
오메프라졸	100	100	100	100	100	100	100	100
β-CD	329	329	657	657	329	329	657	657
수산화나트륨	11.6	23.2	11.6	23.2	11.6	23.2	11.6	23.2

* 단위 : mg

즉, 3성분의 구성비(오메프라졸 : β-CD : 수산화나트륨)를 1:1:1, 1:1:2, 1:2:1, 1:2:2의 4종류의 비율로 하여서 고체분산체와 물리적 혼합물의 경우에 대해 각각 제조한 것이다.

[제조예 4]

오메프라졸-HPCD-수산화나트륨 고체분산체 및 물리적 혼합물의 제조

다음 표 13의 처방으로 제조예 2의 방법에 따라 고체분산체 및 물리적 혼합물을 제조하였다. 다만 수산화나트륨을 용해하기 위하여 정제수 5ml를 추가하였다.

[표 13]

제제물의 조성

성분(mg)	고체분산체		물리적 혼합물	
	9	10	11	12
오메프라졸	100	100	100	100
HPCD	376	376	376	376
수산화나트륨	11.6	23.2	11.6	23.2

즉, 3성분의 구성비(오메프라졸 : HPCD : 수산화나트륨)를 1:1:1, 1:1:2의 비율로 하여서 각각 제조한 것이다.

[실험예 3]

제조예 3과 4의 제제물에 대하여 용출시험을 실시하여 각각의 제제물의 특성을 비교 평가하였다. 용출시험방법은 실험예 1의 방법과 동일하게 하여 그 결과는 다음 표 14에 나타내었다.

조성비율이 다른 여러 종류의 고체분산체(제제물 1~4, 제제물 9~10)가 모두 단순히 혼합한 물리적 혼합물(제제물 5~8, 제제물 11~12) 보다 높은 용출률을 나타낼 수 있다.

[표 14]

제제물 1~12의 용출시험결과

제제물	용 출 률(%)				
	1분	3분	5분	10분	20분
제제물 1	84.46	94.93	92.23	91.81	92.32
제제물 2	94.40	98.11	96.14	94.83	94.81
제제물 3	92.81	98.80	97.97	99.05	99.00
제제물 4	90.75	92.00	95.46	99.30	99.62
제제물 5	27.86	42.50	44.63	54.26	63.10
제제물 6	48.52	55.25	58.58	63.28	70.63
제제물 7	35.16	44.35	52.23	59.80	64.79
제제물 8	37.31	45.81	48.66	57.14	66.28
제제물 9	98.01	99.98	98.90	99.97	99.54
제제물 10	97.97	98.03	99.87	99.34	99.87
제제물 11	38.18	43.04	48.13	56.20	65.46
제제물 12	58.92	61.44	64.27	71.29	74.37

[실험예 4]

제조에 3과 4의 제제물에 대하여 이들의 경시보존 안정성을 향상시키고자 방습제를 첨가하여 방습제의 첨가효과를 시험하였다.

제조에 3과 4의 제제물 1, 2, 3, 4, 9, 10에 방습제로 탄산마그네슘, 산화마그네슘을 제제물 1중량부일 때 각각 0.5중량부씩 첨가하고 균일하게 혼합하였다.

이 제제물을 순서대로 제제물 a, b, c, d, e, f로 명명하고 이 제제물의 경시변화시험과 용출시험을 하여 방습제 첨가에 의한 안정화 효과와 용출률의 영향을 비교 평가하였다. 비교 대조군으로는 오메프라졸 단독의 오메프라졸 1중량부, 탄산마그네슘 0.5중량부 및 산화마그네슘 0.5 중량부의 혼합물(오메프라졸+방습제로 칭함)을 준비하여 기존의 방법에 따라 제조한 것을 시험대상으로 하였다.

경시변화시험은 40℃, 40℃-75% RH, 60℃의 3조건에서 개방상태로 보존하면서 생상의 변화를 측정하였다. 방습제로 첨가한 탄산마그네슘의 배합비율의 범위를 결정하기 위하여 제조에 3의 제제물 2를 1중량부로 하고 여기에 탄산마그네슘 0.3 중량부, 0.5중량부, 1중량부, 2중량부로 각각 혼합하여 40℃-75% RH조건에서 개방상태로 보존하면서 경시변화를 시험하였다.

용출시험결과를 다음 표 15와 같으며, 이때의 용출시험방법은 상기 실험예 1과 동일한 방법으로 실시하였다.

[표 15]

제제물의 용출에 미치는 방습제의 영향

제제물	용출률(%)				
	1분	3분	5분	10분	20분
제제물 a	63.10	72.69	77.64	99.18	99.09
제제물 b	65.41	78.54	80.57	83.57	90.10
제제물 c	55.09	60.79	77.00	84.81	93.46
제제물 d	52.70	64.72	79.93	94.50	97.09
제제물 e	62.31	94.92	94.21	97.26	98.01
제제물 f	87.56	99.41	98.97	98.03	99.85
오메프라졸+방출제	10.26	13.18	16.51	29.31	44.20

3주 동안의 경시변화시험을 변색시험은 다음 표 16과 같다.

[표 16]

방출제를 첨가한 제제물의 경시변색시험 결과

제제물	40℃			40℃-75% RH			60℃		
	1주	2주	3주	1주	2주	3주	1주	2주	3주
제제물 a	A	A	A	A	A	A	A	A	A
제제물 b	A	A	A	A	A	A	A	A	A
제제물 c	A	A	A	A	A	A	A	A	A
제제물 d	A	A	A	A	A	A	A	A	A
제제물 e	A	A	A	A	A	A	A	A	A
제제물 f	A	A	A	A	A	A	A	A	A
오메프라졸+방출제	A	C	C	C	D	E	B	C	D
탄산마그네슘 0.3	A	A	A	A	A	A	A	A	A
탄산마그네슘 0.5	A	A	A	A	A	A	A	A	A
탄산마그네슘 1.0	A	A	A	A	A	A	A	A	A
탄산마그네슘 2.0	A	A	A	A	A	A	A	A	A

* A : 백색 또는 변화 없음, B : 옅은 유백색, C : 유백색, D : 옅은 갈색, E : 갈색

용출시험결과를 보면 산화마그네슘이나 탄산마그네슘과 같은 방출제가 더 추가되더라도 용출률의 변화는 크게 변화되지 않았다. 이러한 결과는 β -CD나 HPCD와 같은 시클로덱스트린류와의 고체분산체에 산화마그네슘이나 탄산마그네슘과 같은 의약품 첨가물이 가해지더라도 용출률이 확보됨과 동시에 표 9에서와 같이 보존안정성이 증대됨을 나타낸다.

또한, 40℃-75% RH에서도 거의 변색을 나타내지 않은 점은 종래의 방법에서는 오메프라졸의 보존안정성을 확보하기 위해 함유수분율 1.5% 이하로 유지하여야 하는 점에 비하여 본 발명의 조성물은 보다 높은 함유조건에서도 안정하기 때문에 제제화가 용이할 뿐만아니라 경시안정성을 높일 수 있다.

[제조예 5]

종래의 기술로 제조한 경우용 오메프라졸의 코어 조성물과 비교하기 위하여 대한민국 특허공고 제91-4579호의 방법으로 오메프라졸 과립을 제조하였다. 또한 본 발명의 방법으로 제조한 고체분산체를 적당한 의약품 첨가물을 이용하여 과립을 제조하였다.

[비교과립 1]

오메프라졸 15g, 유당 119g, L-HPC 5g, 탄산마그네슘 15g을 혼합하고 히드록시프로필셀룰로오스 1g을 무수알콜 30g에 녹인 결합제로 반죽하여 과립을 제조하고 건조하였다.

[비교과립 2]

오메프라졸 20g, 라울릴황산나트륨 0.5g, 인산이수소나트륨 0.8g을 정제수 44g에 현탁시키고 별도로 마니톨 162g, 무수유당 8g, 히드록시프로필셀룰로오스 8g, 미세결정셀룰로오스 4g를 혼합한 것과 반죽하여 과립을 제조하고 건조하였다.

[비교과립 3]

본 발명으로 제조한 실시예 3의 제제를 2를 이용하였다. 제제를 2 90.5g(오메프라졸로서 20g), L-HPC 35g, 유당 24g, 탄산마그네슘 46g을 혼합하고 별도로 히드록시프로필셀룰로오스 5g을 무수알콜 50g에 녹인 결합제로 반죽하여 과립을 제조하고 건조하였다.

[실험예 5]

상기 제조에 5의 방법으로 제조한 세가지 과립에 대하여 실험예 1의 방법과 동일하게 용출시험을 하였고 그 결과는 다음 표 17과 같다.

종래 기술의 방법으로 만든 과립들의 용출성보다 본 발명의 과립의 용출성이 현저히 높게 나타났다. 본 발명의 과립은 1분대에 약 80%가, 분대에는 거의 100%가 용출되었다.

이러한 결과는 본 발명의 고체분산체가 경구용 오메프라졸 보어의 수송능력을 확보할 수 있는 수단임을 증명해 주는 것이다.

[표 17]

비교과립의 용출률

비교과립	용 출 률(%)				
	1분	3분	5분	10분	20분
1	24.71	44.31	47.94	65.62	80.45
2	48.87	66.61	73.00	83.61	89.76
3	87.48	94.47	99.01	98.96	99.61

또한 실험예 1과 같은 방법으로 경시변색시험을 하여 안정성을 비교하였고, 그 결과는 다음 표 18과 같다. 여러 보존조건에서 보관한 과립의 경시변색 특성은 본 발명의 조성물을 이용한 과립이 제조초기와 아무런 변화를 나타내지 않았다.

그러나 종래의 기술로 제조한 과립들은 40℃~75% RH에서 3주 후에 유백색-갈색으로 변색되었다.

[표 18]

비교과립의 경시 변색시험결과

비교과립	40℃			40℃~75% RH			60℃		
	1주	2주	3주	1주	2주	3주	1주	2주	3주
1	A	A	B	C	C	C	A	B	C
2	A	B	C	C	D	E	A	C	D
3	A	A	B	A	B	C	A	B	C

* A : 백색 또는 연하 없음, B : 많은 유백색, C : 유백색, D : 많은 갈색, E : 갈색

이상의 결과로 볼때 제 1항의 조성물은 경시보통 안정성과 용해성이 매우 높은 경구용 오메프라졸의 코어 조성물을 제공한다.

(57) 청구의 범위

청구항 1. 오메프라졸을 유효성분으로 하고, 여기에 안정화 성분으로 베타-시클로덱스트린을 혼합시켜서 경구용 오메프라졸 약제의 코어 조성물을 제조함에 있어서, 유효성분인 오메프라졸에다 안정화 성분으로서 베타-시클로덱스트린 또는 그 유도체와 함께 수산화나트륨을 첨가 혼합시켜서 고체분산체로 제조함을 특징으로 하는 경구용 오메프라졸 약제의 코어 조성물을 제조하는 방법.

청구항 2. 제1항에 있어서, 베타-시클로덱스트린 유도체로는 히드록시프로필-베타-시클로덱스트린을 사용함을 특징으로 하는 경구용 오메프라졸 코어 조성물을 제조하는 방법.

청구항 3. 제1항에 있어서, 상기 베타-시클로덱스트린 또는 그 유도체는 오메프라졸 1몰에 대하여 0.5몰 내지 2몰로 첨가시킴을 특징으로 하는 경구용 오메프라졸 코어 조성물을 제조하는 방법.

청구항 4. 제1항에 있어서, 상기 알칼리 화합물은 오메프라졸 1몰에 대하여 0.5몰 내지 2몰로 첨가시킴을 특징으로 하는 경구용 오메프라졸 코어 조성물을 제조하는 방법.



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INPADOC Record

Title: KR9611238B1: OMEPRAZOLE PREPARATION AND ITS PROCESS

Country: KR Republic of Korea

Kind: B1 Examined Patent Application, Second Publication; since 970930 Granted Patent

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Issued/Filed Dates: Aug. 21, 1996 / July 5, 1993

Application Number: KR1993000012580

IPC Class: A61K 31/415; A61K 31/44;

ECLA Code: none

Priority Number(s): July 5, 1993 KR1993000012580

Abstract:

The acid-resistant omeprazole preparation is composed of a medicine layer containing omeprazole; and an enteric coating layer containing enteric polymer. It is particularly prepared by introducing a concentration gradient in one layer or both layers of the medicinal substance layer and the enteric coating layer. The more outer, the thinner the concentration of the medicinal substance layer is. And the more outer, the denser the concentration of the enteric polymer is.



Family: none

Fact Info: DERABS C1999-284997 DERABS C1999-284997

References: No patents reference this one

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A61K 31 /415

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박사릉

시간 : 61월 29
(특허공보 제 4675호)

(54) 산에서 불안정한 화합물의 경구 제형 및 그 제조방법

요약

내용없음.

도면

1

상세

[발명의 명칭]

산에서 불안정한 화합물의 경구 제형 및 그 제조방법

[도면의 간단한 설명]

개1도는 본 발명에 의한 최종제형이 과립제인 경우의 단면도이다.

개2도는 본 발명에 의한 제형의 약물함유층의 농도구배를 나타낸다.

개3도는 본 발명에 의한 제형의 장용피층의 농도구배를 나타낸다.

[발명의 상세한 설명]

본 발명은 오메프라졸을 함유하는 새로운 안정화 경구 제형 및 그 제조방법에 관한 것이다.

산분비에 관하여는 프로톤 펌프를 저해하여 강력한 위산분비 억제작용을 가지고 있는 오메프라졸, 5-메톡시-2-[[[4-메톡시-3,5-디메틸-2-피리디닐] 술폰릴]-1H-벤조이미다졸은 최근 새로운 위 및 십이지장질환 치료제로 주목받고 있다. 그러나 오메프라졸은 알칼리 조건 하에서는 안정하지만 산 또는 중성 매질 하에서는 쉽게 분해, 변형되어 그 약효를 상실하기 쉽다. 예를 들면, pH값이 4미만의 수용액에서 오메프라졸의 반감기는 10분 미만이고, pH값이 7에서 그것의 반감기는 약14시간이나, pH값이 7보다 높은 용액에서의 안정성은 보다 증가한다(Pilbrant Cederberg의 Scand. J. Gastroenterology 1985, 20(Suppl. 108) pp113-120).

그러므로, 오메프라졸의 안정화 경구 약제는 오메프라졸이 산성 위액에서 분해되지 않고 통과하여 소장에도달할 수 있도록 설계되어야 한다. 그리고, 오메프라졸 약제에서 오메프라졸의 용출 속도가 오메프라졸의 흡수량에 영향을 주므로, 복강시에 위를 통과해야 할 뿐만 아니라 장에서 유효성분이 신속하게 방출할 수 있는 형태이어야 한다.

오메프라졸의 통상적인 제조 방법인 대한민국 특허공고 제91-45789호에서는 오메프라졸과 안정화제를 첨가하여 펠릿를 제조하고, 수난용성 폴리머를 분리층을 피복시킨 후 최종적으로 장용피층을 형성시켜 오메프라졸을 제조하는 방법이 기술되어 있다. 그러나 이 방법에 의한 오메프라졸 제제는 오메프라졸과 첨가제를 혼합하여 혼합, 습윤, 압출, 건조, 입자선폭 등의 과정을 거친 후에야 펠릿가 제조되고, 이를 다시 내피층을 1차 코팅하고 그 위에 장용피로 2차 코팅을 하는 등의 복잡한 과정을 거친 후 캡슐에 충전하여야 한다. 따라서, 공정도 복잡할 뿐만 아니라 작업시간도 긴 단점이 있다.

또한, 대한민국 특허공보 제91-2041호에서도 오메프라졸을 함유하는 핵에 수난용성 피막물질과 수난용성 세립물질로써 이루어진 물질로 중간 피복층을 입히고 그 위에 장용성 막을 피복하는 방법, 즉 2회 코팅방법을 도입하고 있어 작업이 복잡하고 그에 따른 수용 하락의 문제점이 있다.

상기와 같은 문제점을 해결하기 위하여 본 발명자들은 구배 코팅(gradient coating)방법을 연구하였다. 기존의 오메프라졸 경구 약제들이 약물함유층과 장용피층 사이에 내피층(또는, 중간 피복층)을 두는 이유가 오메프라졸 함유 코어에 직접 장용피층이 코팅되면 장용피층의 산성특성이 오메프라졸과 접촉하여 산에 의한 오메프라졸을 분해, 퇴색시키기 때문이라는 데 착안하여 이를 해결하는 방법을 연구하였다. 본 발명자들은 유동층 코팅 장치 및 서클레이트를 이용하여 조성 상의 구배를 만들면서 한 공정상에서 연속 코팅하여 내피층 또는 중간피복층이 필요없는 최종 제형을 만들어냄으로써 내산성 및 보관안정성이 우수하며 오메프라졸의 분해가 일어나지 않으면서도 기존의 방법에 의해 제조공정이나 작업시간이 짧고 비용이 높은 경구제형을 만들 수 있다는 사실을 발견하여 본 발명을 완성하게 되었다.

본 발명은 오메프라졸을 약물로 함유하는 약물함유층에 장용폴리머를 함유하는 장용층을 코팅하는 오메프라졸의 경구 제형에 있어서, 약물함유층, 장용피층의 어느 한층 또는 두 층 모두에서 약물함유층의 오메프라졸 및 장용피층의 장용폴리머가 그 내부와 외부 사이에 농도의 구배를 갖도록 하여 보다 안정화되고, 하나의 제조공정으로 간편히 제조되는 새로운 오메프라졸의 경구 제형 및 그 제조방법을 제공하는 것을 목적으로 한다.

본 발명의 경구 제형은 오메프라졸을 알칼리성 안정화제와 알칼리성 또는 중성 결합제를 함유하는 혼합물을 이용하여 제형화 허용되는 부형제 분말과 함께 코어를 만들되, 중심 부분에서 외부로 갈수록 오메프라졸의 함량이 감소하여 결국에는 오메프라졸의 함량이 0이 되고, 그 시점에서부터 바로 장용폴리머를 조금씩 입히기 시작하여 최종에는 장용폴리머의 함량이 80% 이상이 되도록 연속 코팅된다. 본 발명의 핵심인 조성을 연속적으로 구배시키는 방법은 적용하는 기계장치에 따라서 세립제, 과립제, 정제 등에 공히 적용할 수 있으며, 또한 캡슐제에도 적용할 수 있다.

본 발명에 사용되는 성분으로는 오메프라졸, 오메프라졸 안정화제, 결합제, 부형제, 작용폴리머, 가소제, 유화제, 무기첨가물 등이 사용된다. 자세하게는 오메프라졸의 안정화제로 기존의 제산제, 약산의 무기염, 약산의 유기염, 열기성 아미노산 등을 사용할 수 있다. 예를 들면, 수산화알루미늄, 수산화칼륨, 수산화마그네슘, 탄산마그네슘, 탄산알루미늄, 인산알루미늄, 인산칼슘, 인산나트륨, 인산칼륨, 스테아르산 칼슘, 스테아르산칼슘, 스테아르산마그네슘, 시트르산알루미늄, 시트르산칼슘, 시트르산나트륨, 시트르산칼륨, 산화마그네슘, $Al_2O_3 \cdot 6MgCO_3 \cdot 12H_2O$, $MgAl_2(OH)_4CO_3 \cdot 4H_2O$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot H_2O$, 아르기닌, 리진, 히스티딘, 무수규산, 규산칼슘, 수크로스, 지방산에스테르 등을 단독 또는 혼합하여 사용할 수도 있으며, 더욱이 본 발명에서는 N-메틸글루카민, 글루코스아민과 같은 아미노슈가 및 카프릭산, 라우릭산 등의 지방산의 나트륨염, 칼슘염, 칼슘염, 마그네슘염 중에서 선택된 단일염 또는 그 혼합물을 사용하였다. 이들 중에서 특히, N-메틸글루카민을 사용하는 것이 바람직하다.

결합제 및 부형제는 제약상 허용되며 물에 신속히 분해하는 것은 어느 것이나 사용할 수 있으며, 바람직하게는 결합제로는 하이드록시프로필셀룰로스나 하이드록시프로필메틸셀룰로스를 사용하고, 부형제로는 만니톨을 사용하는 것이 적당하다. 작용폴리머로는 메타크릴산과 메타크릴산메틸에스테르의 공중합체(쥘파르마사의 Eudragit, FMC 코오포레이션사의 Aquateric, 바스프사의 Coating CE 5142), 셀룰로오스아세테이트프탈레이트, 하이드록시프로필메틸셀룰로스프탈레이트, 폴리아크릴아세테이트프탈레이트, 카르복시메틸에틸셀룰로스, 하이드록시프로필메틸셀룰로스아세테이트속시네이트, 폴리아크릴산유도체, 왁진산 등을 사용할 수 있으며, 바람직하기로는 하이드록시프로필메틸셀룰로스아세테이트속시네이트, 메타크릴산과 메타크릴산메틸에스테르의 공중합체가 적당하다. 가소제로는 세틸알코올, 스테아릴알코올, 트리아세틴, 시트르산에스테르, 프탈산에스테르, 디부틸속시네이트, 디부틸프탈레이트, 디에틸프탈레이트, 에틸렌글리콜모노에틸에테르, 폴리에틸렌글리콜, 디메틸폴리실록산, 프로필렌카보에이트, 트리에틸시트레이트와 같은 제약상 허용되는 것 또는 이와 유사한 가소제를 임의로 사용할 수가 있으며, 이들 가소제를 사용하지 않을 수도 있다. 또한, 유화제로는 소듐라우릴설페이트, 소듐비탄에스테르류 등을 사용할 수도 있고, 사용하지 않을 수도 있다.

본 발명은 더욱 자세히 설명하면 다음과 같다.

백당

백은 코팅 씨드를 제공하기 위한 백당 결정으로 조성의 구배가 없고 그 크기는 100마이크로미터에서 2000마이크로미터 사이의 크기이며, 바람직하기로는 600마이크로미터에서 710마이크로미터사이(32-24메쉬)가 적당하다.

약물함유층

본 발명에서 약물함유층이란 백 및 작용층을 제외한 오메프라졸 함유층을 칭하는 것으로, 오메프라졸, 안정화제, 결합제, 부형제 등으로 이루어져 있으며, 오메프라졸 안정화제로 위에서 기술한 것과 같은 알칼리 첨가물을 모두 적용할 수 있으나, 바람직하게는 N-메틸글루카민, 글루코스아민과 같은 아미노슈가 또는 카프릭산, 라우릭산 등의 지방산의 나트륨염, 칼슘염, 칼슘염, 마그네슘염을 단독 또는 혼합 사용하여 소량의 수분을 첨가하였을 경우, pH값 8이상의 환경을 만들어준다. 결합제 및 부형제는 제약상 허용되며 물에 신속히 분해되는 것을 사용하며, 바람직하게는 결합제로 하이드록시 프로필 셀룰로스나 하이드록시프로필메틸셀룰로스를 사용하고 부형제로는 만니톨을 사용하는 것이 적당하다. 여기서 약물함유층은 오메프라졸의 농도 구배가 중심부에서 외부로 갈수록 얇게 주어져 있어서 약물함유층의 가장 외부에는 오메프라졸이 포함되어 있지 않고 안정화제, 결합제, 부형제 등으로 이루어져 있으며, 유화제를 첨가할 수도 있다. 약물함유층의 두께는 원하는 과립제의 크기에 따라 임의로 정할 수 있으나, 바람직하게는 100마이크로미터에서부터 1000마이크로미터 두께가 적당하다.

작용피층

본 발명에서 작용피층이란 작용폴리머가 포함된 층을 칭하는 것으로 작용폴리머, 결합제, 가소제, 유화제, 무기첨가물 등으로 이루어져 있다. 작용폴리머는 상기한 것들을 모두 적용할 수 있으나, 바람직하게는 하이드록시프로필메틸셀룰로스아세테이트속시네이트, 메타크릴산과 메타크릴산메틸에스테르의 공중합체가 적당하다. 결합제는 제약상 허용되며 물에 신속히 분해되는 것을 사용하며 바람직하게는 하이드록시프로필셀룰로스나 하이드록시프로필메틸셀룰로스를 사용하는 것이 적당하다. 무기첨가물로는 활석이나 산화티타늄이 적당하다. 가소제 및 유화제로는 상기한 것들을 모두 적용할 수 있으나 적용하지

양을 수도 있다. 장용층의 두께는 10마이크로미터에서부터 500마이크로미터 사이가 적당하며, 10마이크로미터보다 얇은 경우 위액이 투과되어 오메프라졸이 분해 변색되며 500마이크로미터보다 두꺼울 경우 약물이 장액에서 신속하게 방출되지 않는다. 바람직하게는 20 마이크로미터에서 100마이크로미터 사이가 적당하며, 더욱 바람직하게는 40마이크로미터에서 60 마이크로미터 사이가 적당하다.

최종제형

본 발명에 의한 최종 제형의 모양을 제1도에 나타내었다(과립제의 경우). 제형에 따라서 핵은 없을 수도 있다.

제1도에서 보는 바와 같이, 본 발명의 경구 제형은 핵, 약물함유층, 장용피층으로 이루어져 있다. 핵은 코팅 씨드를 제조하기 위한 백당 결정으로 조성의 구배가 없으나, 약물함유층은 오메프라졸의 농도 구배가 중심에서 외부로 갈수록 열게 되어져 있고, 장용피층은 장용폴리머의 농도 구배가 중심에서 외부로 갈수록 진하게 주어져 있다. 이러한 농도 구배는 약물함유층 및 장용피층의 어느 한 층에만 도입될 수도 있고, 두 층 모두에 도입될 수도 있다.

장기간의 보관안정성을 얻기 위하여 오메프라졸의 최종제형의 수분함량을 낮게 유지시키는 것이 중요하며, 바람직하게는 수분 함량이 1.0중량%를 초과하지 않는 것이 좋다.

구배코팅방법

로터리형 유동장치(Glatt GPCG1)에 약제 투입시 서클레이터를 통하여 주입하되 서클레이터에 마이크로 펌프를 통하여 연속적으로 구배용액 투입량을 증가시킨다. 여기서 구배용액이란 약물함유층의 경우에 오메프라졸이 포함되어 있지 않은 안정화제, 결합제, 부형제 등의 용액이며, 장용피층의 경우에는 장용폴리머 용액이다.

본 구배 코팅 방법에 의해 구배된 오메프라졸 함량은 구형과립의 중심으로부터 제2도에 나타낸 바와 같은 분포를 가질 때 가장 바람직하다.

또한, 장용폴리머는 약물함유층으로부터 제3도와 같은 분포를 가질 때 가장 바람직하다.

이하, 본 실시예는 본 발명의 특성을 보다 자세히 설명하는 것이며, 본 발명의 범위를 제한하는 것은 아니다. 여기서 모든 양과 비율은 중량기준이다.

실시예 1

약물함유층의 조성에는 특별한 제한은 없으나 로터리형 유동장치(Glatt GPCG1)를 사용하기 위해서는 더욱 조성이 적당하였다.

오메프라졸의 경구제형을 제조하기 위하여 500~710마이크로미터(32~43메쉬) 크기의 백당 결정을 로터리형 유동장치에 넣고 모터를 300rpm으로 회전시켰다. 그리고, 만니톨 분말(입자 크기 : 100마이크로미터 이하)을 분당 12그램씩 투입하면서 아래의 조성으로 이루어진 분산용액을 분당 8ml씩 분무하여 오메프라졸을 코팅시켰다.

(1)와 동시에 연속적으로 다음과 같은 구배 용액의 투입량을 증가시켰다.

구배용액 조성 : 오메프라졸 12

N-메틸플루카민 1

하이드록시프로필셀룰로스 2

수용라우릴술페이트 0.3

전유수 88

당니를 분말 100

배양액 조성 : N-메틸글루카민 1

하이드록시프로필셀룰로스 2

소듐라우릴설페이트 0.3

물 88

당니를 분말 100

배양액 조성으로는 다음 조성을 적용하였다.

배양액 조성 : 하이드록시프로필셀룰로스 10

탄산 13

디에틸프탈레이트 0.3

물 1000

배양액 조성 : 하이드록시프로필셀룰로스-

아세트산시네이트 10

탄산 8

디에틸프탈레이트 0.3

물 1000

이때의 제조 기기 및 운전조건은 다음과 같았다.

장치 : GPO를 구비한 Glatte GPGI, 분무노즐 : 1.0mm 노즐방향 : 절선방향, 유입공기온도 : 30~40℃, 공기유입속도 : 4.5~6.5m/s, 로터디스크속도 : 250~360rpm, 펌프속도 : 10l/min

실시에 2

이제 운전조건은 실시예1 과 같으며, 적용 조성은 다음과 같았다.

배양액 조성 : 오메프라졸 12

글루코사민 1

하이드록시프로필셀룰로스 2

트윈80(분산제의 상품명) 0.3

물 88

당니를 분말 100

주배용액 조성 : N-메틸글루카민

1

히드록시프로필메틸셀룰로스 2

3원 80 0.3

전류수 66

만니톨 분말 100

장용피층 조성으로 다음 조성을 적용하였다.

코팅용액 조성 : 히드록시프로필메틸셀룰로스 10

완성 13

디에틸프탈레이트 0.3

전류수 1000

주배용액 조성 : 메타크릴산과 메타크리산

디에스테르의 공중합체 10

완성 5

디에틸시트레이트 0.3

전류수 1000

비교실시예 1

(아래의 조성물질을 중 건조성분(A)을 먼저 혼합하고, 오메프라졸을 함유하는 과립화액상물(B)을 건조성분에 첨가하여 습식 혼합하고, 젖은 덩어리를 압출기를 통하여 압착하여 구형화시켜 펠릿으로 만들었다.

건조성분(A) : 만니톨 66

락로스 무수물 3

히드록시프로필셀룰로스 3

미세결정성 셀룰로스 2

과립화 액상물(B) : 오메프라졸 8

스름라우릴술페이스 0.2

인산수소이나트륨 0.3

전류수 18

(아래의 분리층(C) 코팅용액으로 유동층 장치에서 분리층을 코팅하고 난 후, 장용피 코팅용액(D)으로 35~40마이크로미터

단계로 코팅하여 오메프라졸 과립을 제조하였다.

내피층 코팅용액(C) : 히드록시프로필메틸셀룰로스- 5

정류수 95

장용피층 코팅용액(D) : 히드록시프로필메틸- 10

셀룰로스프탈레이트

개릴알코올 1

탄올 90

비교실시예 2

원조성분 및 과립액상물의 조성은 비교실시예 1과 같고 내피층 및 장용피층의 코팅용액 조성은 다음과 같고 장용피층의 두께는 35~40마이크로미터로 하였다.

내피층 코팅용액(C) : 폴리비닐피롤리돈 10

고수락토스 200

탄올 90

디데아르산마그네슘 2

장용피층 코팅액(D) : 유드라젯L30D 30

디부틸프탈레이트 1

탄산 5

산화티타늄 1

정류수 70

시험예 1 : 내산성 시험

실시예 및 비교실시예에서 제조된 장용성 오메프라졸 과립을 대한 약전에 기술되어 있는 대로 제1용액에 넣고 37℃, 150rpm의 속도로 패킷을 사용하여 내산성 시험을 하여 1시간 간격을 각 과립의 외관을 관찰하였다. 그 결과는 다음 표 1과 같다.

[표 1]

시료 \ 시간	1시간	2시간	3시간
실시예 1	백색	백색	백색
실시예 2	백색	백색	백색
비교실시예 1	백색	백색	갈색
비교실시예 2	백색	백색	갈색

실시예에서는 제조된 광용성 과립은 3시간 동안 내산성 시험후에도 변화가 없었으나 비교실시예의 경우 3시간 후에는 갈색을 변화하였다.

실험예 2 : 보관안정성 시험

상의 실시예 및 비교실시예에서 제조된 광용성 오메프라졸 과립을 40℃, 상대습도 75%의 조건에서 5일 및 10일간 저장하고 각 광용성 오메프라졸 과립의 외관을 관찰하였다. 그 결과 다음의 표 2와 같았다.

[표 2]

시료 \ 보관기간	5일	10일
실시예 1	백색	백색
실시예 2	백색	백색
비교실시예 1	백색	갈색
비교실시예 2	백색	갈색

실시예 1 및 2에서 제조된 각각의 오메프라졸 과립은 보관 기간 10일 후에도 변화가 없으나, 비교실시예 1 및 2의 경우에는 10일 보관후에 색상이 갈색으로 변화하였다.

실험예 3 : 오메프라졸 함량비교 시험

안정화 효과를 비교하기 위하여 각 과립을 40℃, 상대습도 75%의 조건에서 7일간 보관한 다음, HPLC를 이용하여 과립 중에 남아있는 오메프라졸의 함량을 측정하였다. 그 결과는 다음 표 3과 같았다.

[표 3]

시료	평균함량(%)
실시예 1	97
실시예 2	98
비교실시예 1	86
비교실시예 2	89

이상의 결과로부터, 구배 코팅이 기존의 두 층 코팅보다 오메프라졸 안정화효과가 뛰어나를 알 수 있다.

3.7 청구의 범위

청구항 1. 오메프라졸을 약물로 함유하는 약물함유층에 장용폴리머를 함유하는 장용층을 코팅한 오메프라졸의 경구 제형에 있어서, 약물함유층 및 장용층의 어느 한 층 또는 두층 모두에 농도 구배를 도입하며, 이때, 약물함유층의 농도구배는 오메프라졸의 농도가 중심에서 외부로 갈수록 얇게 주어지고, 장용층의 농도구배는 장용폴리머의 농도가 중심에서 외부로 갈수록 진하게 주어진 것을 특징으로 하는 오메프라졸 경구 제형.

청구항 2. 제1항에 있어서, 약물함유층 내에 백당 결정의 코어가 존재함을 특징으로 하는 오메프라졸 경구 제형.

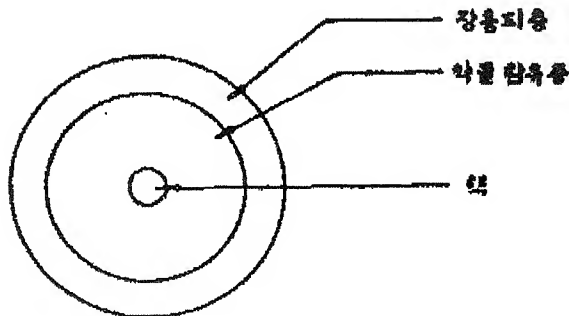
청구항 3. 제1항 내지 제3항에 있어서, 약물함유층의 두께가 100~1000 μ m임을 특징으로 하는 오메프라졸 경구 제형.

청구항 4. 제1항 또는 제2항에 있어서, 장용층의 두께가 10~50 μ m임을 특징으로 하는 오메프라졸 경구 제형.

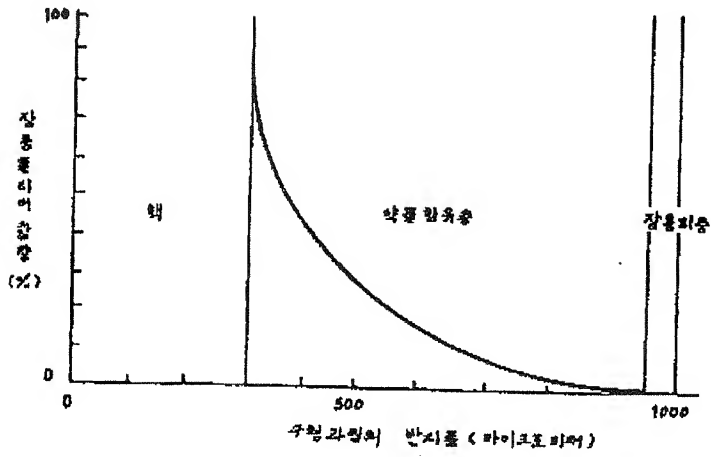
청구항 5. 오메프라졸을 약물로 함유하는 약물함유층에 장용폴리머를 함유하는 장용층을 코팅한 오메프라졸 경구 제형의 제조방법에 있어서, 약물함유층 및 장용층의 어느 한 층 또는 두층 모두에 농도 구배를 도입하며, 이때, 약물함유층은 오메프라졸의 농도가 중심에서 외부로 갈수록 얇게 주어진 농도 구배를 갖도록 코팅하고, 장용층은 장용폴리머의 농도가 중심에서 외부로 갈수록 진하게 주어진 농도 구배를 갖도록 코팅함을 특징으로 하는 오메프라졸 경구 제형의 제조 방법.

도 1

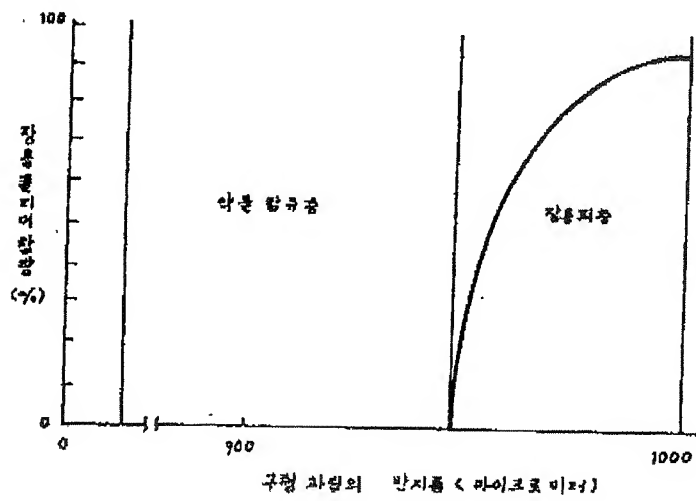
도면 1



도면 2



도면 3





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INPADOC Record

Title: **KR9611390B1: PROCESSES FOR PREPARATION OF BENZIMIDAZOLE DERIVATIVES**

Country: **KR Republic of Korea**

Kind: **B1 Examined Patent Application, Second Publication; since 970930 Granted Patent**

Inventor(s): **KIM, SANG - HO, Republic of Korea
BAEK, SUNG - INN, Republic of Korea
KIM, KI - SUK, Republic of Korea**

[No Image](#)

Applicant/Assignee

KOLON IND. INC., Republic of Korea
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Inquire Regarding Licensing

Issued/Filed Dates

Aug. 22, 1996 / April 28, 1993

Application Number

KR1993000007197

IPC Class

C07D 401/12;

ECLA Code

none

Priority Number(s)

April 28, 1993 KR1993000007197

Abstract

The method for preparing 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridyl)methyl sulfinyl benzimidazol of formula (I) comprises reacting a compound of formula (II) with an aniline derivative of formula (III) using a metal catalyst in a nonpolar-aprotic solvent to obtain a compound of formula (IV), and oxidatively cyclizing a compound of the formula (IV) to obtain a benzimidazol derivative of formula (I).



Family

none

Other Abstract Info

DERABS C1999-285100 DERABS C1999-285100

Foreign References

No patents reference this one

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(12) 특허공보(B1)

(51) Int. Cl. 6		(11) 등록번호	특1996-0011390
G07D 401 / 12		(24) 등록일자	1996년08월22일
(21) 출원번호	특1993-0007197	(65) 공개번호	특1999-0000001
(22) 출원일자	1993년04월28일	(43) 공개일자	1999년01월01일
(73) 특허권자	주식회사코오롱 하기주 서울특별시 중구 무교동 45번지		
(72) 발명자	김상호 경기도 부천시 원종동 삼신아파트 다중 401호 백성인 경기도 용인군 구성면 진주빌라 302 김기석 경기도 수원시 팔달구 매탄동 삼성아파트 2차 1동 207호		
(74) 대리인	박사중		

사관 : 이만복
(특허공보 제490호)

(54) 벤조이미다졸 유도체의 제조방법

요약

내용 없음.

제1서

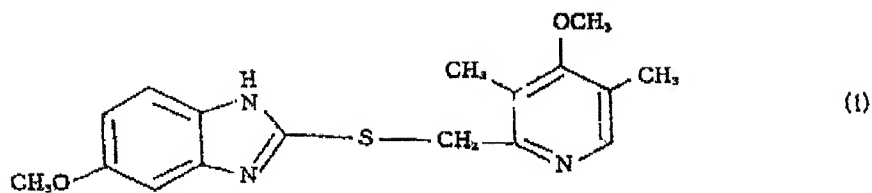
[발명의 명칭]

벤조이미다졸 유도체의 제조방법

[발명의 상세한 설명]

본 발명은 벤조이미다졸 유도체, 특히, 암지의 화합물로서 위산분비를 억제하며 위궤양, 십이지장궤양 및 위염을 포함하는 위장질환의 치료에 유용한 다음 구조식(1)의 5-메톡시-2-[[[4-메톡시-3,5-디메틸-2-피라릴]메탄설폰아미드]벤조이미다졸을 제조하는 방법에 관한 것이다.

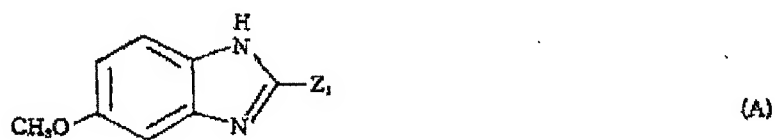
[도식]



상기 구조식(1)의 화합물을 제조하는 공지의 방법은 미합중국특허 제4,182,788호, 제 4,255,431호 및 제4,472,409호, 일본공개특허 제 57-53,406호, 제 58-39,622호, 대한민국공개특허 제 84-1156호 등에 기술되어 있는데 이들 제조방법을 살펴보면 다음과 같다.

1. 다음 일반식(A)의 벤조이미다졸 유도체와 일반식(B)의 피리딘 메틸 유도체를 반응시켜서 구조식(1)의 화합물을 제조하는 방법.

식 2



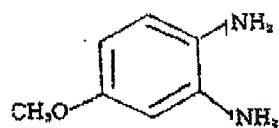
식 3



(여기서, Z₁, Z₂ 중 하나는 머캅토기(SH)이고, 다른 하나는 반응성 에스테르화기이다.)

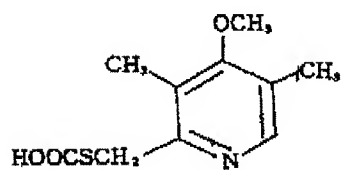
2. 다음 일반식(C)의 o-페닐렌디아민 유도체와 일반식(D)의 피리딘산 유도체를 반응시켜 구조식(1)의 화합물을 제조하는 방법.

1. 화학식 4



(C)

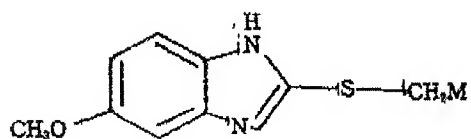
1. 화학식 5



(D)

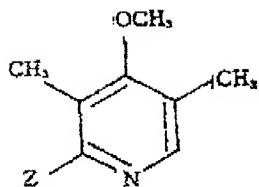
3. 다음 일반식(E)의 벤조이미다졸 유도체와 일반식(F)의 피리딘 유도체를 반응시켜 구조식(1)의 화합물을 제조하는 방법

1. 화학식 6



(E)

1. 화학식 7



(F)

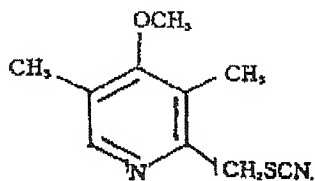
(식중, M은 금속으로 칼륨, 나트륨, 리튬이고 Z는 반응성 에스테르와 히드록시기이다.)

앞에서 살펴본 공지의 제조방법은 일반식(D)나 (E)와 같이 반응출발물질의 제조가 매우 어렵거나 또는 중간체 화합물이 불안정하기 때문에 목적화합물의 제조수율이 극히 저조한 문제점이 있으며, 머캄토벤조이미다졸 유도체 등은 고가의 화합물인 관계로 경제성이 떨어지는 단점이 있다.

이에, 본 발명은 상기의 제조방법과는 상이하면서 보다 경제적이고 제조공정이 용이하고 목적화합물의 수율이 크게 개선된 새로운 제조방법을 제공하는데 그 목적이 있다.

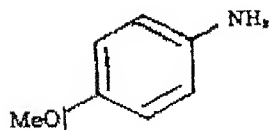
본 발명은 벤조이미다졸 유도체류 제조함에 있어서, 다음 구조식(II)의 피리딘 유도체와 구조식(III)의 아닐린 유도체류 반응시켜서 다음 구조식(IV)의 아미딘 유도체를 제조하고, 제조된 구조식(IV)의 화합물을 N-클로로화반응을 통해 다음 구조식(V)의 반응중간체를 제조한 후 계속적으로 산화적 고리화반응(Oxidative Cyclization)을 통해서 상기 구조식(I)의 목적 화합물을 제조할 수 있는 경제적인 제조방법을 제공한다.

화학식 8



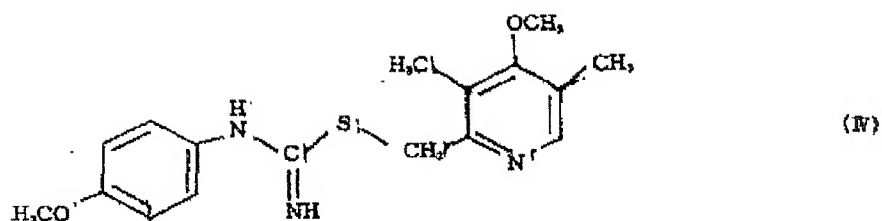
(II)

화학식 9

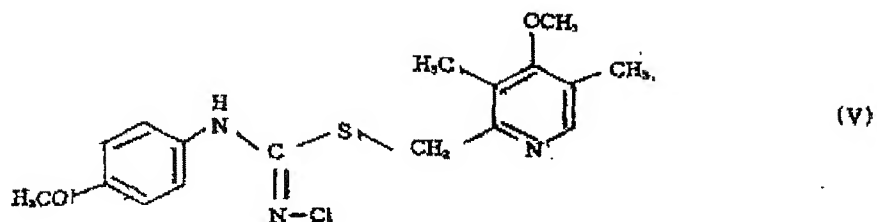


(III)

· 화식 10



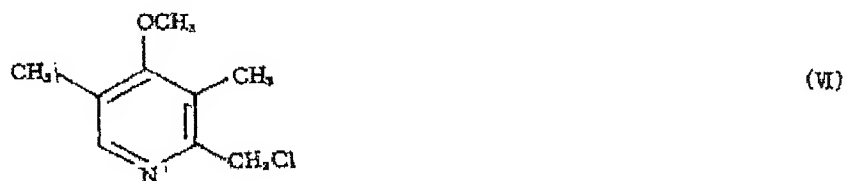
· 화식 11



(이하, 본 발명을 상세히 설명한다.)

본 발명에 있어서, 출발물질인 구조식(II)의 피리딘 메틸 티오시아네이트 유도체는 공지 방법에 의하여 제조되는 바, 공지의 화합물인 다음 구조식(VI)의 3,5-디메틸-4-메톡시-2-할로메틸피리딘과 다음 구조식(VII)의 티오시아네이트를 에탄올, 메탄올, 이소프로필 알코올 등과 같은 알코올 용매에서 반응시켜 용이하게 제조할 수 있다. 상기의 반응에서 반응용매로는 에탄올이 가장 좋으며 티오시아네이트로는 소듐 티오시아네이트, 포타슘 티오시아네이트 또는 알모늄 티오시아네이트를 사용할 수 있다.

· 화식 12



[화식 13]

MSCN

(VI)

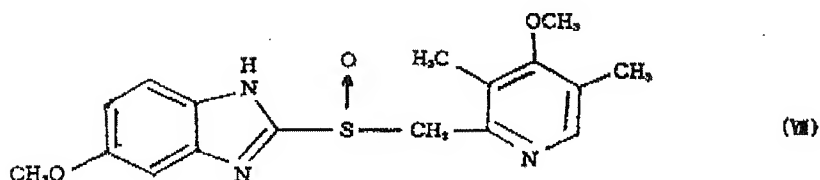
[비고, M은 Na, K 또는 NH₄를 나타낸다.]

상기와 같이 제조한 구조식(II)의 화합물을 디클로로메탄, 디클로로에탄 또는 테트라클로로에탄과 같은 비극성 비양자성 용매 중에서 알루미늄 클로리드를 사용하여 구조식(III)의 2-메톡시아닐린과 1~3시간 동안 환류반응시켜서 구조식(IV)의 화합물을 높은 수율로 얻는다. 이때, 알루미늄 클로리드는 상기 구조식(III) 화합물 1당량에 대하여 1~3당량을 사용할 수 있으나, 바람직하게는 1~1.7당량을 사용하는 것이 좋다. 또한, 상기 구조식(IV)의 화합물은 하이드로 클로리드의 부가물로 수득하는 것이 더욱 좋다.

상기의 반응을 통해서 제조한 구조(IV)의 화합물을 디클로로메탄과 같은 비극성 비양자성 용매와 묽의 혼합용매중에서 소량 소량 하이포클로리트와 20℃ 내지 50℃에서 반응시켜 구조식(V)의 화합물을 제조하고, 이 화합물을 알코올과 묽의 혼합용매중에서 수산화나트륨, 수산화칼륨 등과 같은 알칼리 화합물과 1 내지 2시간 동안 환류반응시켜서 목적화합물인 상기 구조식(1)의 벤조이미다졸 유도체를 높은 수율로 얻게 된다. 상기 반응에 있어서 소량 하이포클로리트는 상기 구조식(IV)의 화합물 1당량에 대하여 1 내지 2당량 사용하는 것이 좋으나 더욱 좋기로는 1 내지 1.3당량을 사용하는 것이 바람직하다. 상기 구조식(IV)의 화합물로부터 상기 구조식(1)의 벤조이미다졸 유도체를 얻기 위해서 더욱 좋기로는 구조식(V)의 N-클로로카르복사미딘 유도체를 분리하지 않고 계속적으로 반응시키는 바, 상기 구조식(IV)의 화합물을 50% 메탄을 수용액에서 소량 하이포클로리트와 상온에서 반응시켜 N-클로로카르복사미딘 유도체를 중간체로 얻고 여기에 탄산나트륨 포화 수용액을 가한 후 1 내지 2시간 동안 환류반응을 진행시켜 목적화합물인 상기 구조식(1)의 벤조이미다졸 유도체를 수득하는 것이 바람직하다.

상기의 본 발명에 의한 공정을 통해서 얻어지게 되는 상기 구조식(1)의 벤조이미다졸 유도체를 과산화제를 사용하여 공지의 방법으로 산화시키면 약반명이 오메프라졸인 다음 구조식(VII)의 벤조이미다졸 유도체가 얻어진다.

[화식 14]



이와 같이, 본 발명은 공지의 제조방법과는 제조공정이 상이할 뿐 아니라, 수율이 매우 높고 공정이 용이하며 또한, 매우 저가의 출발물질들을 사용하는 관계로 경제성이 뛰어난 특징이 있다.

(이하, 본 발명을 실시예 등에 의거하여 더욱 상세히 설명하면 다음과 같으며, 본 발명이 다음 실시예에 의해 한정되는 것은 아니다.

[참고예 1]

5-(디메틸-4-메톡시-2-티오시아노메틸피리딘 (II)의 제조

3,5-디메틸-4-메톡시-2-티클로로메틸피리딘 37.2g(0.2몰)을 에탄올 250ml에 넣고 5℃ 정도의 저온에서 소량 티오시(4네이트 17.84g(0.22몰)을 30분간에 걸쳐 서서히 가한 후 30분간 교반한 후 반응온도를 올려 3 내지 5시간 동안 환류반응을 시켰다. 반응이 종결되면 식온으로 냉각하고 생성된 염화나트륨을 여과하여 제거한 후 용매를 감압하에 증류시켰다. 잔사에 물과 메틸렌클로라이드를 가하여 증분리를 한 후 유기층을 모아서 무수 황산마그네슘으로 건조시키고 용매를 감압증류하여 표제의 화합물 40.82g(98%)을 얻었다.

원소분석치($C_{10}H_{12}N_2OS$)

이론치 : C : 57.67, H : 5.80, N : 13.45

실측치 : C : 57.69, H : 5.83, N : 13.64

[실시예 1]

1). N-(4-메톡시페닐)-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]카복복사민(IV)의 제조

4-메톡시아닐린 25그램(203밀리몰)과 3,5-디메틸-4-메톡시-2-티오시아노메틸피리딘 42.3그램(203밀리몰)을 테트라하드로에탄 200밀리리터에 넣어 용해한 후 상온에서 알루미늄 클로라이드 27.1그램(203밀리몰)을 첨가하고 1시간 동안 환류반응을 시켰다. 반응이 완결되면 반응용액의 온도를 상온으로 낮춘 후 과량의 5N 수산화나트륨 수용액을 가하여 반응중 생성된 알루미늄 클로라이드 부산물을 분해하고 여기서 생성된 수산화알루미늄을 증류수 200밀리리터를 첨가하여 용해하고 여기에 메틸렌클로라이드 150밀리리터를 가하여 증분리를 시켰다.

여기에서 얻어진 유기층을 증류수로 세척한 후 무수 황산마그네슘으로 건조시키고 용매를 감압증류하여 표제의 화합물 61.0그램(92%)을 얻었다.

원소분석치($C_{17}H_{21}N_3O_3S$)

이론치(%) : C : 61.6, H : 6.39, N : 12.69

실측치(%) : C : 61.71, H : 6.43, N : 12.73

2). N-클로로-N'-(4-메톡시페닐)-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]카복복사민(V)의 제조

N-(4-메톡시페닐)-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]카복복사민 30그램(90밀리몰)을 상온에서 증류수와 메틸렌클로라이드 1:1 혼합용액 150밀리리터에 넣고 교반하면서 여기에 31.3밀리리터의 2.88M 소량 하이포클로리트를 첨가하고 1시간 동안 상온에서 반응을 진행시킨 후 증류수와 메틸렌클로라이드를 사용하여 증분리를 하고 여기에서 얻어진 유기층을 무수 황산마그네슘으로 건조시킨 후 감압증류하여 표제의 화합물 32.23그램(96%)을 얻었다.

원소분석치($C_{17}H_{19}ClN_3O_3S$)

이론치(%) : C : 55.81, H : 5.51, N : 11.48

실측치(%) : C : 55.84, H : 5.53, N : 11.51

6). 5-메톡시-2-[[[2-(4-메톡시-3,5-디메틸)피리딘]메틸]티오]벤조아미다졸(1)의 제조

실시예 1-2)에서 얻어진 N-클로로-N'-(4-메톡시페닐)-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]카복사민 30그램 (92밀리몰)을 50% 메탄올 수용액에 넣고 여기에 3.5그램의 수산화나트륨 수용액 10밀리리터를 가하여 1시간 동안 환류반응을 시켰다. 반응이 완결된 후 반응액의 온도를 상온으로 내린 후 묽은 염산으로 pH를 6으로 조정하고 메틸렌클로라이드와 증류수를 사용하여 유기층을 층분리시켜 무수 황산마그네슘으로 건조하고 감압증류하여 목적화합물인 표제의 25.2그램 (83%)을 얻었다.

1H NMR(CDC₃/TMS) ppm(δ) : 2.23(3H,s), 2.30(3H,s), 3.77(3H,s), 4.38(2H,s), 6.78-7.61(3H,s), 8.18(1H,s)

[실시예 2]

5-메톡시-2-[[[2-(4-메톡시-3,5-디메틸)피리딘]메틸]티오]벤조아미다졸(1)의 제조

실시예 1-1)에서 얻어진 N-(4-메톡시페닐)-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]카복사민 30그램(90밀리몰)을 50% 메탄올 수용액 200밀리리터에 넣고 교반하면서 상온에서 2.88M의 소듐하이포클로라이트 31.3밀리리터(90밀리몰)를 가한 후 1시간 동안 상온에서 교반하여 중간체인 구조식(V)의 N-클로로카복사민 유도체를 제조하고 계속적으로 여기에 12.4그램의 탄산나트륨 포화수용액을 첨가하여 1시간 동안 환류반응을 시켰다. 반응이 완료된 후 반응온도를 상온으로 내린 후 증류수와 메틸렌클로라이드를 사용하여 유기층을 분리시키고 유기층을 무수황산마그네슘으로 건조하고 감압증류하여 목적화합물인 표제의 화합물 29.05그램(98%)을 얻었다.

[참고예 2]

5-메톡시-2-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]벤조아미다졸(VIII)의 제조

상기 실시예 2에 따라 제조된 5-메톡시-2-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]벤조아미다졸 24.9그램 (75.6밀리몰)을 메틸렌클로라이드 200밀리리터에 녹이고 반응용액의 온도를 -30℃로 조정하였다. 여기에 탄산수소나트륨 포화수용액 70밀리리터를 첨가하고, 75% 메타클로로퍼옥시벤조익산 17.68그램(75.6밀리몰)을 메틸렌클로라이드 50밀리리터에 녹인 용액을 동일온도에서 1시간 동안 적가한 후 반응온도를 서서히 0℃로 올려서 40분 동안 교반하였다. 반응이 완료된 후 탄산수소나트륨 포화수용액과 메틸렌클로라이드를 각각 100밀리리터씩 넣고 유기층을 분리한 후 무수 황산마그네슘으로 탈수시키고 여과하여 감압증류시켰다. 이와 같이 얻은 잔사에 아세트과 이소프로필에테르를 가하여 결정화시켜 백색 결정의 표제화합물(VIII) 22.7그램(87%)을 얻었다.

1H NMR(CDC₃) : ppm(δ) : 2.17(3H,s), 2.21(3H,s), 3.59(3H,s), 3.41(3H,s), 4.82(2H,s), 6.79-7.82(3H,s), 8.20(1H,s)

[비교실시예 1]

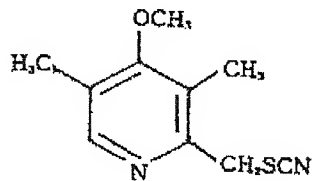
5-메톡시-2-[[[2-(3,5-디메틸-4-메톡시)피리딘]메틸]티오]벤조아미다졸의 제조

대한민국 특허공고 88-1714호에 기재된 실시예의 외거하여, 3,5-디메틸-4-메톡시-2-클로로메틸피리딘 염산염 22.2그램(0.1몰)과 5-메톡시-2-머캅토 벤조아미다졸 17.9그램(0.1몰)을 메탄올 250밀리리터에 용해시킨 후 이 용액에, 증류수 25밀리리터에 용해시킨 수산화나트륨 4그램(0.1몰)을 첨가하고 이 혼합물을 6시간 동안 환류시킨 후 냉각하고 여기에 증류수 500밀리리터를 가해서 희석시켰다. 생성된 혼합물에 메틸렌클로라이드를 첨가해서 추출하고 건조 및 증발시킨 후 잔류물을 아세트니트릴을 사용해서 재결정하여 유리 열기형으로 표제의 물질 25.7그램(73%)을 얻었다.

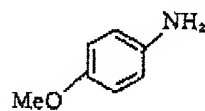
1) 청구의 범위

청구항 1. 다음 구조식(II)의 화합물을 비극성 비양자성 용액중에서 금속촉매를 사용하여 다음 구조식(III)의 아날린

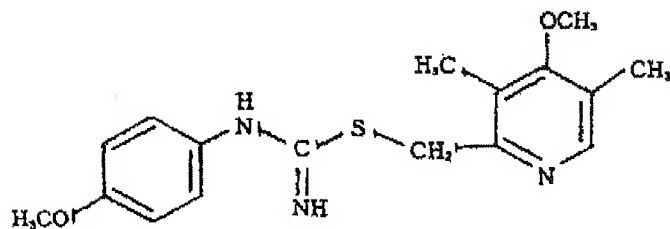
유도체와 반응시켜 다음 구조식(IV)의 화합물을 제조하고, 이 화합물을 산화적 고리화반응(Oxidative Cyclization)을 시켜 다음 구조식(I)의 벤즈이미다졸 유도체를 제조하는 방법.



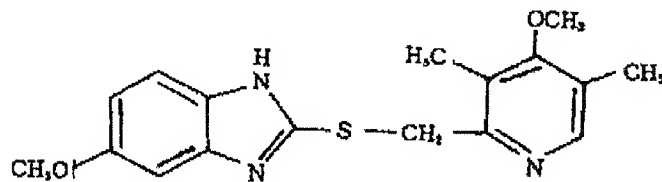
(II)



(III)



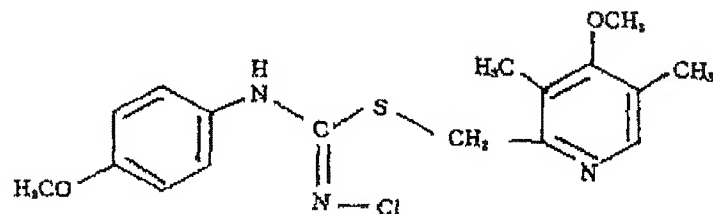
(IV)



(I)

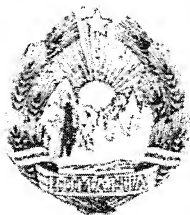
원구항 2. 제1항에 있어서, 금속촉매가 알루미늄클로라이드인 것을 특징으로 하는 방법.

원구항 3. 제1항에 있어서, 산화적 고리화반응시 다음 구조식(V)의 중간체를 거쳐 연속반응(in-situ)으로 상기 구조식(I)의 화합물을 제조하는 것을 특징으로 하는 방법.



(V)

원구항 4. 제3항에 있어서, 소듐 하이포클로라이드를 사용하여 상기 구조식(V)의 중간체를 제조하는 것을 특징으로 하는 방법.



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Compoziție pentru tratamentul afecțiunilor gastroduodenale

1

Invenția se referă la o compoziție pentru tratamentul afecțiunilor gastroduodenale și este complementară la invenția cu descrierea nr. 65970, și anume pentru tratarea afecțiunilor gastroduodenale ca gastrite, gastroduodenite, ulcere gastroduodenale, ulcere complicate cu stenoze piloro-duodenale funcționale, sindrom Zollinger-Ellison, tratamentul medical al hemoragiilor digestive superioare.

Este cunoscut faptul că afecțiunile digestive superioare, afecțiuni cu etiopatologie complexă, de cele mai multe ori necunoscută, devin manifeste clinic prin creșterea secreției gastrice acide. Depășirea limitelor critice individuale ale secreției acidului clorhidric conduce la depășirea capacității de apărare a mucoaselor gastroduodenale (secreția gastrică alcalină, secreția de mucus, bariera mucoasei gastrice, secreția alcalină pancreatico-biliară) și, implicit, la apariția și persistența sindromului de tip ulceros.

Instalarea unui proces hipersecretor continuu pe fondul scăzut al factorilor de apărare conduce, prin activarea pepsinei, la procese erozive gastroduodenale de tipul nișelor (ulcerațiilor) sau perforațiilor. Moda-

5

litățile terapeutice actuale urmăresc, cu mici excepții, reducerea secreției gastrice acide, creind astfel condiții de regenerare a leziunilor și de restabilire a factorilor de protecție.

Dintre aceste modalități pot fi menționate următoarele:

10

a) neutralizarea acidului clorhidric cu antacide - terapie clasică;

15

b) terapia cu blocanți ai receptorilor colinergici:

- terapia cu anticolinergice vizând eliminarea factorilor de stimulare neurovegetativi și SNC (Atropina, Pro-Banthine, Pirenzepin etc.);

20

- terapia cu antagoniști ai receptorilor H_2 -histaminici (Cimetidina, Ranitidina, Oxmetidina etc.);

25

c) terapia antienzimatică cu inhibitori ai ATP-azei K. H-dependentă (Omeprazole, Picoprazole), inhibitori ai histidindecarboxilazei etc.;

d) terapia cu blocanți ai influxului intracelular de calciu (Nifedipin, Varapamil etc.).

Dintre excepții menționăm terapia clasică cu pansamente gastrice, terapia cu factori de stimulare a secreției de mucus

(Carbenoxolone), terapia cu factori citoprotectori (PGE_2 , PGI_2 etc.) și terapia cu agenți de acțiune locală (Sucralfat, Tricitrat bipotasice de bismut etc.).

Dezavantajul acestor metode constau fie într-o eficacitate redusă (procentele de vindecare variind între 35 și 80%), hipersecreție reactivă postterapeutică (antacide), durata îndelungată și costul ridicat al agenților terapeutici și, mai ales, în procentul ridicat al recidivelor.

Introducerea metodei de tratament al afecțiunilor gastroduodenale cu inhibitori ai anhidrazei carbonice descrise în invenția principală a rezolvat, în cea mai mare parte, aceste dezavantaje, prin utilizarea unei compoziții având cea mai ridicată și cea mai rapidă eficacitate terapeutică alături de cel mai redus procent de recidive.

Inconveniente rămase nerezolvate de compoziția și metoda descrisă anterior sînt legate de existența, în anumite cazuri, a unei perioade de latență de 2-5 zile, perioada necesară instalării fenomenului de inhibiție, în care manifestările clinice dure-roase pot persista. De asemenea, dozele zilnice de administrare sînt destul de ridicate și, cu toate că efectele secundare sînt eliminate prin asocierile de factori compensatori, utilizarea compoziției este contraindicată în unele afecțiuni renale grave.

Introducerea metodei de tratament a afecțiunilor gastroduodenale cu inhibitori ai anhidrazei carbonice a fost posibilă ca urmare a următoarelor fundamentări teoretice:

— descoperirea anhidrazei carbonice — Meldrum și Roughton 1933;

— descoperirea implicării enzimei în lanțul biochimic clorhidrosecretor la nivelul celulei parietale — Davenport — 1938. S-a stabilit astfel că prin catalizarea reversibilă a reacției:

$\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-$
enzima intervine în mecanismul secreției de acid clorhidric furnizînd intracelular ioni de hidrogen necesari formării intraluminale a acidului clorhidric. Reacția, decurgînd și necatalizată la un nivel care poate asigura desfășurarea normală a acestui proces, cercetările au rămas la nivelul unei informații științifice;

— descoperirea inhibitorilor specifici ai anhidrazei carbonice de tipul sulfonamidelor tiadiazolice și benzotiazolice — Keillin și Mann 1980;

— descoperirea posibilității de reducere a secreției gastrice acide, prin inhibiția enzimei la animale — Ianovitz-Colcher și Hollander, 1952;

— stabilirea faptului că anhidraza carbonică intervine în lanțul biochimic secretor al acidului clorhidric la nivelul celulei parietale, ca o etapă esențială, determinată de viteză — Pușcaș, 1981;

— stabilirea faptului că administrarea de inhibitori în doze și perioade care să realizeze o inhibiție de peste 80% a activității enzimei de mucoasă gastrică umană conduce la instalarea anacidității interprandiale și pe parcursul repausului secretor conturînd anaciditate caracteristică secreției gastrice bazale; stabilirea dozei minime eficiente — Pușcaș, 1971;

— descrierea existenței fenomenului de activare prelungită a anhidrazei carbonice la pacienții cu afecțiuni gastroduodenale ca element etiopatogenetic — Pușcaș, 1972-1974;

— descrierea modalităților de eliminare și limitare a efectelor secundare caracteristice dozelor eficiente de inhibitori ai anhidrazei carbonice, doze esențiale pentru instalarea unui efect antisecretor eficient — Pușcaș, 1972-1974;

— demonstrarea, în clinica umană, a modalității de tratament a afecțiunilor gastroduodenale cu etiopatogeneza hipersecretorie, prin instalarea unei anacidități bazale interprandiale și pe parcursul repausului secretor nocturn, proces realizat ca urmare a inhibiției anhidrazei carbonice din mucoasa gastrică umană — Pușcaș, 1971-1977;

Compoziția descrisă de invenția principală asociază un inhibitor de anhidrază carbonică cu bicarbonați de sodiu și potasiu pentru compensarea pierderilor electrolitice urinare, citrat de sodiu sau de potasiu ca factor compensator profilactic, împotriva scăderii citraturiei pe parcursul administrării inhibitorului, oxid sau carbonat de magneziu ca factor sistemic anticalcic și adjuvant cu acțiune sinergică inhibitorului la nivelul enzimei și, opțional, hidroxid de aluminiu ca factor profilactic renal și reechilibrare fosfocalcică în situații specifice.

Trebuie menționat faptul că această compoziție este eficientă prin acțiunea sa inhibitorie asupra anhidrazei carbonice și nu necesită pentru realizarea acestui efect o anumită capacitate neutralizantă antiacidă. Administrarea sodiului, potasiului, magneziului și aluminiului în forme bazice s-a efectuat pentru contracararea dezavantajului acestei modalități terapeutice caracterizată de o perioadă de latență definită ca perioadă în care simptomatologia clinică dureroasă a afecțiunilor poate persista, dezavantaj manifest în special la pacienții cu afecțiuni în puseu acut. Mai mult, pe lângă faptul că asocierea la inhibitor a unei capacități de neutralizare antiacidă nu realizează decît parțial acest deziderat, administrarea bicarbonaților reprezintă un dezavantaj prin faptul că prelungeste perioada de instalare a fenomenului diuretic, iar administrarea magneziului în formula anorganică este inferioară administrării sub forma compușilor organici.

Compozițiile, conform invenției complementare, conțin următoarele: inhibitor — de

- anhidrază carbonică de tip sulfonamidic;
 -- săruri de sodiu și potasiu;
 -- săruri anorganice și organice de magneziu;
 -- hidroxid sau săruri organice de aluminiu;
 -- săruri minerale de acid citric;
 -- oligoelemente;
 -- neuroleptice;
 -- antidepresive tricyclice;
 -- inhibitori ai influxului intracelular de calciu;
 -- inhibitori de ATP-aza K, 11 - dependente;
 -- antagoniști ai receptorilor H₂-histaminici;
 -- anticolinergice;
 -- agenți cu acțiune locală.

În invenția principală inhibitorii de anhidrază carbonică eficienți în tratamentul acțiunilor gastroduodenale sînt acetazolamida, metazolamida, benzolamida, etoxzolamida la care se adaugă și benzotiazol-2-sulfonamida.

Compoziția, conform invenției, perfecționează invenția principală cu descrierea nr. 65970 prin aceea că este constituită din (părți): 0,25...1,8 acetazolamidă, 0,1...1,4 bicarbonat de sodiu, 0,1...3,17 bicarbonat de sodiu, 0,1...3,17 bicarbonat de potasiu, 2,25...4,5 oxid de magneziu, 0,29...0,58 citrat de sodiu, 0,42...1 hidroxid de aluminiu, asociate cu metazolamida 0...1,8 benzenamidă, 0...1,8 benzotiazol-2-sulfonamida 0...

3,6 etoxzolamida, 0...0,95 ca atare sau sub formă de săruri de K, Na, Al, Zn sau 0...1,8 săruri de Na, K, Mg, Al, Zn ale acetazolamidelor, 0...2,31 săruri de Na și K ale acizilor lactic, malic, pantotenic, gluconic, precum și alte oligoelemente, 0...4,5 cu Zn, Mg, Ca, Cu, Ni, Co, Mn sub formă de săruri ale acizilor sulfurici, lactic, glicinic, aspartic, citric, pantotenic, gluconic, alantoinic, asociate cu neuroleptice sau antidepresive ca 0...0,076 fenobarbital, 0...0,5 fluanaxol, 0...0,2 amitriptilină, 0...0,7 levomepromazin, 0...0,8 stazepin, 0...1,17 cimetidina, 0...0,15 ranitidină, 0...0,03 nifedipină, 0...0,06 omeprazol, precum și 0...0,01 pEE₂, 0...0,36 alantoină, 0...1,4 carbonat de bismut, 0...0,030 atropină, 0...0,27 papaverină, 0...0,03 propantilină, părțile fiind exprimate în greutate.

Se descriu în continuare compoziții eficiente în tratamentul afecțiunilor gastroduodenale în care cantitățile de ingrediente sînt exprimate, cu mici excepții, în mmol, fiecare compoziție reprezentînd unitatea de doză pentru 20 Kg corp/zi, cu efect echivalent unei compoziții standard de acetazolamida descrisă de invenția principală.

A. Modalități de administrare per os a componentelor utile din compoziția standard.

a) Inhibitorii de anhidrază carbonică pot fi administrați în forma liberă sau săruri minerale de sodiu, potasiu, magneziu, aluminiu, zinc, cupru, nichel, cobalt, mangan etc.

Exemplul	1	2	3	4	5
acetazolamidă	1,8	0	0	0	0
metazolamidă	0	1,8	0	0	0
benzolamidă	0	0	1,8	0	0
benzotiazol-2-sulfonamidă	0	0	0	3,6	0
etoxzolamidă	0	0	0	0	0,95
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,2
oxid de magneziu	4,5	4,5	4,5	4,5	4,5
citrat de sodiu	0,58	0,58	0,58	0,58	0,4
hidroxid de aluminiu	1	1	1	1	1

Exemplu	1	6	7	8	9	10	11	12
acetazolamidă	1,8	0	0	0	0	0	0	0
bicarbonat de sodiu	0,6	0	0,6	0	0,35	0,35	0	0
bicarbonat de potasiu	1,55	0,35	1,55	0	1,25	0	0	0
citrat de sodiu	0,58	0,58	0,58	0,58	0,58	0,58	0,58	0,4
oxid de magneziu	4,5	4,5	2,7	4	4,5	4,5	3,05	4,5
hidroxid de aluminiu	1	1	1	0	1	1	1	1
acetazolamidă-sodiu	0	0,6	0	0,3	0	0	0	0
acetazolamidă-potasiu	0	1,2	0	0,3	0	0	0	0
acetazolamidă-magneziu	0	0	1,8	0,5	0	0	0	0
acetazolamidă-aluminiu	0	0	0	0,3	0	0	0	0
acetazolamidă-zinc	0	0	0	0,1	0	0	0	0
metazolamidă-potasiu	0	0	0	0	1,55	0	0	0
benzolamidă-potasiu	0	0	0	0	0	1,55	0	0
benzotiazol-2-sulfonamidă-K	0	0	0	0	0	0	1,55	0
etoxzolamidă-potasiu	0	0	0	0	0	0	0	0,95
benzotiazol-2-sulfonamidă-Na	0	0	0	0	0	0	0,6	0
benzotiazol-2-sulfonamidă-Mg	0	0	0	0	0	0	1,45	0
metazolamida-sodiu	0	0	0	0	0,25	0	0	0
benzolamida-sodiu	0	0	0	0	0	0,25	0	0

a₂) Sodiul poate fi administrat sub formă de săruri anorganice sau organice

Exemplul	1	13	14	15	16	17	18
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8	1,8
bicarbonat de sodiu	0,6	0	0	0	0	0	0
bicarbonat de potasiu	1,55	1,55	0	0	0	0	1,5
citrat de sodiu	0,58	0,58	0	0	0	0	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	1	1	1	1
clorură de sodiu	0	0,6	2,34	0	0	0	0
lactat de sodiu	0	0	0	0	0,5	0	0
malat de sodiu	0	0	0	0	0,5	0	0
pantotenat de sodiu	0	0	0	0	0,4	0	0
gluconat de sodiu	0	0	0	0	0	2,34	0
acetazolamidă-sodiu	0	0	0	0	0	0	1,8
citrat de potasiu	0	0	0,58	0,58	0,58	0,58	0

a₃) Potasiul poate fi, de asemenea, administrat cu formă de săruri anorganice sau organice

Exemplul	1	19	20	21	22	23	24
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8	0,25
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0,6	0,6	0,6
bicarbonat de potasiu	1,55	0	0	0	0	0	0
citrat de sodiu	0,58	0,58	0,58	0,58	0,58	0,58	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	1	1	1	1
clorura de potasiu	0	1,55	0	0	0	0	0
lactat de potasiu	0	0	1,55	0	0	0	0
malat de potasiu	0	0	0	0	1,55	0	0
gluconat de potasiu	0	0	0	0	0	1,55	0
acetazolamidă-potasiu	0	0	0	0	0	0	1,55

a₄) Magneziul poate fi administrat sub formă de săruri anorganice sau organice

Exemplul	1	25	26	27	28	29	30	31	32
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8	1,8	1,8	0
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0,6	2,34	0,6	0,6	0,6
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,55	1,55	1,55	1,55	1,55
citrat de sodiu	0,58	0,58	0,58	0,58	0,58	0	0,58	0,58	0,58
oxid de magneziu	4,5	0	0	0	0	0	0	0	0,7
hidroxid de aluminiu	1	1	1	1	1	1	1	1	1
sulfat de magneziu	0	4,5	0	0	0	0	0	0	0
lactat de magneziu	0	0	3,5	0	0	0	0	0	0
glicinat de magneziu	0	0	0	2,5	0	0	0	0	0
aspartat de magneziu	0	0	0	0	2,5	0	0	0	0
citrat de magneziu	0	0	0	0	2,5	2,5	0	0	0
gluconat de magneziu	0	0	0	0	0	0	2,5	0	0
pantotenat de magneziu	0	0	0	0	0	0	0	3,5	0
acetazolamidă-magneziu	0	0	0	0	0	0	0	0	1,8

a₅) Aluminiul poate fi administrat sub formă de săruri anorganice sau organice

Exemplul	1	33	34	35	36	37	38
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8	0,8
bicarbonat de sodiu	0,6	0,6	0,6	2,34	0,6	0,6	0,6
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,55	1,55	1,55
citrat de sodiu	0,58	0,58	0,58	0	0,58	0,58	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	0	0	0,42	0	0	0
alantoinat de aluminiu	0	1	0	0	0	0	0
pantotenat de aluminiu	0	0	1	0	0	0	0
citrat de aluminiu	0	0	0	0,58	0	0	0
aspartat de aluminiu	0	0	0	0	1	0	0
glicinat de aluminiu	0	0	0	0	0	1	0
acetazolamida-aluminiu	0	0	0	0	0	0	1

a₆) Acidul citric poate fi administrat sub formă de săruri anorganice

Exemplul	1	39	40	41	42	43	44	45	46
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8	1,8	1,8	1,8
bicarbonat de sodiu	0,6	2,34	2,34	2,34	2,34	2,34	2,34	2,34	2,34
bicarbonat de potasiu	1,55	0	1,55	1,55	0,11	0,41	0,71	1	1,31
citrat de sodiu	0,58	0	0	0	0	0	0	0	0
oxid de magneziu	4,5	4,5	3,92	4,5	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	0,42	1	1	1	1	1
citrat de potasiu	0	0,58	0	0	0,48	0,38	0,28	0,18	0,08
citrat de magneziu	0	0	0,58	0	0	0	0	0	0
citrat de aluminiu	0	0	0	0,58	0	0	0	0	0
citrat de zinc	0	0	0	0	0,1	0,1	0,1	0,1	0,1
citrat de cupru	0	0	0	0	0	0,1	0,1	0,1	0,1
citrat de nichel	0	0	0	0	0	0	0,1	0,1	0,1
citrat de cobalt	0	0	0	0	0	0	0	0,1	0,1
citrat de mangan	0	0	0	0	0	0	0	0	0,1

B. Metode de reducere a dozei eficiente de inhibitor

b₁) Asocierea de oligoelemente

Exemplu	1	47	48	49	50	51	52	53
acetazolamidă	1,8	1,26	1,8	1,08	0,9	1,08	0	0
bicarbonat de sodiu	0,6	0,42	1,4	0,36	0,3	0,36	0,42	0,42
bicarbonat de potasiu	1,55	1,08	0,83	0,93	0,775	0,93	1,08	1,08
citrat de sodiu	0,58	0,4	0	0,348	0,28	0,348	0,4	0,4
oxid de magneziu	4,5	3,15	2,7	2,7	2,25	2,7	3,15	3,15
hidroxid de aluminiu	1	0,7	0,6	0,6	0,5	0,7	0,7	0,7
sulfat de zinc	0	2	0	0	0	0	0,8	0
citrat de zinc	0	0	1,5	0	0	0	0	0
glicinat de zinc	0	0	0	1,5	0	0	0	0
aspartat de zinc	0	0	0	0	2,5	0	0	0
gluconat de zinc	0	0	0	0	0	1,5	0	0
gluconat de cupru	0	0	0	0	0	0	0	0,1
gluconat de cobalt	0	0	0	0	0	0	0	0,1
gluconat de nichel	0	0	0	0	0	0	0	0,1
gluconat de mangan	0	0	0	0	0	0	0	0,1
acetazolamidă-zinc	0	0	0	0	0	0	1,26	1,26

b₂) Asocierea de neuroleptice sau antidepresive triciclice

Exemplul	1	54	55	56	57	58
acetazolamidă	1,8	1,53	1,44	1,53	1,53	1,53
bicarbonat de sodiu	0,6	0,51	0,48	0,51	0,51	0,51
bicarbonat de potasiu	1,55	1,32	1,24	1,32	1,32	1,32
citrat de sodiu	0,58	0,49	0,46	0,49	0,49	0,49
oxid de magneziu	4,5	3,8	3,6	3,8	3,8	3,8
hidroxid de aluminiu	1	0,85	0,85	0,85	0,85	0,85
fenobarbital	0	0,076	0	0	0	0
flunxol	0	0	0,3 mg	0	0	0
amitriptilină	0	0	0	0,2	0	0
levomepromazin	0	0	0	0	0,007	0
stecapin	0	0	0	0	0	0,8

b₃) Asocierea de antagoniști ai receptorilor H₂-histaminici, blocați ai influxului intracelular de calciu, inhibitori ai ATP-azei K, H-dependente prostaglandine

Administrare parenterală

Exemplul	1	59	60	61	62	63
acetazolamidă	1,8	1,26	1,26	1,08	1,08	1,08
bicarbonat de potasiu	1,55	1	1	0,93	0,93	0,93
bicarbonat de sodiu	0,6	0,42	0,42	0,36	0,36	0,36
citrat de sodiu	0,58	0,4	0,4	0,35	0,35	0,35
oxid de magneziu	4,5	3,15	1,15	2,7	2,7	2,7
hidroxid de aluminiu	1	0,7	0,7	0,6	0,6	0,6
cimetidină	0	0,58	0	0	0	0
ranitidină	0	0	0,15	0	0	0
nifedipină	0	0	0	0,03	0	0
omeprazole	0	0	0	0	0,03	0
PGE ₂	0	0	50	0	0	0,014

C. Metode de reducere a perioadei de latență

c₁) Asocierea de alcalinizante și pansamente gastrice

Exemplul	1	64	65
acetazolamidă	1,8	1,8	1,8
bicarbonat de sodiu	0,6	0	1,36
bicarbonat de potasiu	1,55	0	3,17
citrat de sodiu	0,58	0	0
oxid de magneziu	4,5	0	0
hidroxid de aluminiu	1	1	6,6
clorură de potasiu	0	1,55	0
clorură de sodiu	0	2,34	0
sulfat de magneziu	0	3,92	0
pantotenat de calciu	0	0	0,34
alantoină 0	0	0	0,36
bismut subcarbonic	0	0	1,4
carbonat de magneziu	0	0	4,75
citrat de magneziu	0	0,58	0
perioada de latență (zile)	2-5	3-5	2-5
frecvența de apariție %	30-40	50-60	30-40

c₂) Asocierea în primele zile de tratament cu neuroleptice sau antidepressive triciclice

Exemplul	1	66	67	68	69
acetazolamidă	1,8	1,8	1,8	1,8	1,8
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0,6
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,55
citrat de sodiu	0,58	0,58	0,58	0,58	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	1	1
fenobarbital	0	0	0,5 mg	0	0
levomepromazin	0	0	0	0,07	0
amitriplină	0	0	0	0	0,2
perioada de administrare (zile)	3	3	3	3	3
perioada de latență (zile)	2-5	2-3	2-3	2-3	2-3
frecvența de apariție %	30-40	25-30	25-30	25-30	25-30

c₃) Asocierea în primele zile de tratament de inhibitori ai influxului intracelular de calciu inhibitori de ATP-aza K. H-dependența antagoniști ai receptorilor H₂-histaminei

Exemplul	1	70	71	72	73
acetazolamidă	1,8	1,8	1,8	1,8	1,8
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0,6
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,55
citrat de sodiu	0,58	0,58	0,58	0,58	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	1	1
nefedipină	0	0,03	0	0	0
omeprazole	0	0	0,06	0	0
cimetidină	0	0	0	0,17	0
ramitidină	0	0	0	0	0,15
perioada de administrare (zile)	3	3	3	3	3
perioada de latență (zile)	2-5	1-21-2	2-3	2-3	2-3
frecvența de apariție	30-40	20-30	20-30	20-30	20-30

c₄) Asocierea în primele zile de tratament de anticolinergice, miorelaxante sau agenți cu acțiune locală

Exemplul	1	74	75	76	77	78
acetazolamidă	1,8	1,8	1,8	1,8	1,8	1,8
bicarbonat de sodiu	0,6	0,6	0,6	0,6	0,6	0,6
bicarbonat de potasiu	1,55	1,55	1,55	1,55	1,55	1,55
citrat de sodiu	0,58	0,58	0,58	0,58	0,58	0,58
oxid de magneziu	4,5	4,5	4,5	4,5	4,5	4,5
hidroxid de aluminiu	1	1	1	1	1	1
antropină	0	0,003	0	0	0	0
papaverină	0	0	0,27	0	0	0
extract de beladonă	0	0	0	1,0 mg	0	0
propantelina	0	0	0	0	0,03	0
sucralfat	0	0	0	0	0	0,0005
perioada de administrare (zile)	—	5	5	5	5	5
perioada de latență (zile)	—	2-5	2-5	2-5	2-5	1-2
frecvența de apariție %	30-40	20-30	20-30	20-30	20-30	15-20

c₅) Administrarea în primele zile de tratament de compoziții cu administrare parenterală pînă la instalarea fenomenului de inhibiție, după care tratamentul se continuă prin administrare per os. De asemenea, reducerea perioadei de latență se poate realiza prin administrarea paralelă a celor două tipuri de compoziții de toată perioada tratamentului.

D. Compoziții pentru administrarea parenterală a inhibitorilor anhidrazei carbonice

Exemplul	1 x	79	80	81	82
acetazolamidă-sodiu	0,6	0,6E	0	0	0,3
acetazolamidă-potasiu	1,2	0,4	0	0	0,3
acetazolamidă-magneziu	0	0	0,9	0,9	0,3
gluconat de magneziu	0	1,5	0	0	0
bicarbonat de sodiu	0	0	0	0	0,1
bicarbonat de potasiu	0,35	0	0	0	0,1
lactat de sodiu	0	0	0,98	0	0,1
lactat de potasiu	0	0	0,66	0	0,4
sulfat de magneziu	0	0	0	0	0,55
citrat de sodiu	0,58	0,18	0,19	0,19	0,19
citrat de potasiu	0	0,12	0,12	0,12	0,12
aspartat de sodiu	0	0	0	0,98	0,1
aspartat de potasiu	0	0	0	0,66	0,02
glicinat de magneziu	0	0	1,05	1,05	0,8
hidroxid de aluminiu	1	0	0	0	0
oxid de magneziu	4,5	0	0	0	0

* Compoziție standard administrată per os.

O modalitate, de asemenea, eficientă, de tratament, se poate realiza prin administrarea parenterală a inhibitorului de anhidrază carbonică paralel cu administrarea orală a celorlalte componente.

Invenția prezintă avantaje prin aceea că, stabilind noi modalități de administrare a unora din componente, reduce sfera contraindicațiilor și, prin asocierea de noi componente sau modificarea metodei de administrare, permite, pe de o parte, reducerea perioadei de latență necesare instalării efectului terapeutic, iar pe de altă parte, permite reducerea dozelor eficiente.

Revendicare

Compoziție medicamentoasă pentru tratamentul afecțiunilor gastroduodenale cu conținut de benzenamidă, bicarbonat de

sodiu, citrat de potasiu, carbonat de magneziu, hidroxid de aluminiu conform invenției principale, cu descrierea nr. 65970, caracterizată prin aceea că este constituită din (părți): 0,25...1,8 acetazolamidă, 0,1...1,4 bicarbonat de sodiu, 0,1...3,17 bicarbonat de potasiu, 2,25...4,5 oxid de magneziu, 0,29...0,58 citrat de sodiu, 0,42...1 hidroxid de aluminiu, asociate cu metazolamidă, 0...1,8 benzenamidă, 1,8 benziazol-2-sulfonamidă, 0...3,6 etoxazolamidă, 0...0,95 ca atare sau sub formă de săruri de K, Na, Al, Zn, sau 0...1,8 săruri de Na, K, Mg, Al, Zn ale acetazolamidei, 0...2,34 săruri de Na și K ale acizilor HCl, lactic, malic, pantotenic, gluconic, precum și alte oligoelemente, 0...4,5 ca Zn, Mg, Ca, Cu, Ni, Co, Mn sub formă de săruri ale acizi-

lor sulfuric, lactic, glicinic, aspartic, citric, pantotenic, gluconic, alantoiniei, asociate cu neuroleptice sau antidepresive ca 0... 0,076 fenobarbital, 0...0,5 fluanxol, 0... 0,2 antitriptilina, 0...0,07 părți levomepromazin, 0...0,8 stazeprin, 0...1,17 cimetidină,

0...0,15 ranitidină, 0...0,03 nifedipină, 0... 0,06 omeprazol, precum și 0...0,01 pGE₂, 0...0,36 alantoină, 0...1,4 carbonat de bismut, 0...0,003 atropină, 0...0,27 papaverină, 0...0,03 propantilină, părțile fiind examinate în greutate.

Președintele comisiei de invenții: ing. Voicu Alexandra

Examinator: ing. Marin Elena



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(21) International Application Number: PCT/SE96/01737 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600071-6 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DEPUI, Helene [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). HALLGREN, Agneta [SE/SE]; Hökegårdsgatan 2C, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE (57) Abstract <p>An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agents or an alginate in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer and an optional separating layer in between the proton pump inhibitor and the enteric coating. The fixed formulation is in the form of multilayered tablets, sachets or multiple unit tableted dosage forms. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with dyspepsia such as heartburn.</p> <div data-bbox="893 1155 1396 1491" data-label="Image"> <p>The diagram shows a cross-section of an oval-shaped tablet. It is divided into several layers. Layer 1 is the outermost layer, indicated by a line pointing to the top edge. Layer 2 is the next layer inward, indicated by a line pointing to the right edge. Layer 7 is the innermost layer, indicated by a line pointing to the center. The tablet contains numerous small circles, representing the multiple unit dosage form.</p> </div>		

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ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the prevention and treatment of dyspeptic symptoms like upper abdominal pain/discomfort and heartburn. The present preparations comprise a combination of different gastric acid suppressing agents, such as an acid susceptible proton pump inhibitor and antacid agent(s) and /or an alginate in a new fixed unit dosage form, especially a
10 tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine, especially in the treatment of dyspeptic symptoms.

Background of the invention

15 Dyspepsia is a common disorders and patients are seeing both gastroenterologists and general practitioners because of it. Heartburn is a symptom of dyspepsia, and it is estimated that 44% of Americans have heartburn at least monthly and some has to contact a doctor about the problem, but only around 25 % of the patients are seeing the doctor because of
20 their dyspepsia problem. Symptoms associated with dyspepsia symptom are for instance upper abdominal pain/discomfort and heartburn, indigestion, sour stomach, heartburn and other gastrointestinal disorders including gastro oesophageal reflux. The wide diversity of symptoms and disease severity produced by gastro oesophageal reflux has led to the need for more individualized treatment strategies.

25 Therapeutic agents effective in the treatment of dyspepsia include gastric acid suppressing agents, such as H₂ receptor antagonists, proton pump inhibitors, other agents of interest are antacids/alkalines and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

WO 95/017080 describes a composition for use in the treatment of for instance heartburn, the composition comprises a H₂ receptor antagonist, such as famotidine, and an alginate and optionally simethicone.

5

Antacid agents and alginates may be used alone in the treatment of heartburn. They have a short duration of action but are seen as inexpensive and safe. Antacid agents work locally through a neutralisation of gastric acid. Alginates further give some mechanical protection against reflux of gastric acid into the oesophagus. The main advantages of antacid agents and alginates are, that they provide fast relief of symptoms. The main disadvantage of antacid agents and alginates is that, dosing has to be repeated frequently to keep the patients free of symptoms, further that antacids in many cases do not provide symptom resolution, i.e. complete relief of symptoms.

15 H₂ receptor antagonists are widely prescribed for reducing gastric acid secretion systemically. Proton pump inhibitors, such as omeprazole, are rapidly taking share from H₂ receptor antagonists. Omeprazole is known to offer significant gain over H₂ receptor antagonists in terms of symptom resolution, healing and prevention of relapse. Proton pump inhibitors provide symptom resolution, but normally not immediately.

20

Proton pump inhibitors have in clinical studies been proven to be very effective in providing symptom resolution (usually within 24 - 48 hours) in patients with dyspepsia associated with gastric ulcers, duodenal ulcers, reflux oesophagitis and gastro oesophageal reflux without oesophagitis. It is for instance established that omeprazole is superior to H₂ receptor antagonists regarding healing of gastroduodenal and oesophageal lesions as well as providing dyspeptic symptom resolution in these conditions, See Eriksson S., Euro Journ of Gastroenterology & Hepatology 1995, 7 : 465.

EP 338861 describes a solid pharmaceutical preparation of an antacid and excipients. It is proposed to use this preparation in combination with a proton pump inhibitor or any other

30

substance inhibit gastric acid secretion. There is no suggestion to combine these substances in one fixed unit dosage form.

US 5 244 670 describes an ingestible pharmaceutical composition comprising a substance
5 selected from the group consisting of antacid agents, acid secretion prevention agents, bismuth-containing agents, and mixtures thereof, and the excipient 3-1-menthoxy propane 1,2-diol. There are no specific arrangements discussed in neither of these references, to solve the problem with one of the component being an acid susceptible proton pump inhibitor.

10 A combination therapy of a proton pump inhibitor and an antacid or an alginate would provide immediate symptom relief, provided by the local effect of the antacid agent or the alginate, combined with a long-lasting symptom resolution provided by the systemically acting proton pump inhibitor. Such a combination would be ideal for "on-demand treatment
15 " of dyspepsia as well as for symptom resolution. The combination therapy comprising an acid suppressing agent, for instance a proton pump inhibitor, together with an antacid agent or an alginate could also be an alternative to each of them separately in case of failure.

It is well known that patient compliance is a main factor in receiving good results in medical
20 treatments. Administration of two or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more active substances combined in one fixed unit dosage form, preferably a tablet.

25 Some gastric acid suppressing agents, such as proton pump inhibitors, are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that the one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the

prior art, see for example US-A 4,786,505 (AB Hässle) describing a preparation comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets comprising an acid susceptible proton pump inhibitor as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, layered formulations comprising an enteric coating layered tablet core, multilayered tablets or a sachet filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor and antacid agents. Alternatively, in some of the formulations the antacid agents may be replaced by an alginate. These new dosage forms will simplify the regimen and improve the patient compliance.

Brief description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with antacid agent(s) and pharmaceutical excipients(2). Optionally, the tablet is covered by a filmcoating layer, i.e. tablet coat (7).

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprising a mixture of pharmaceutical excipients and an antacid agent(s) or an alginate (2). Optionally the layers are separated by an anti-tacking layer. Further the tablet is optionally covered by a filmcoating layer (7).

Fig. 3 illustrates a cross-section of a tablet comprising a mixture of pharmaceutical excipients and an acid susceptible proton pump inhibitor in the tablet core (5) surrounded by of an enteric coating layer (8) optionally with a separating layer applied in between the tablet core and the enteric coating layer and upon the enteric coating layer a layer of the antacid agent(s) in admixture with pharmaceutical excipients (6). Optionally, the tablet is covered by a filmcoating layer (7).

Detailed description of the invention

15

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antacid agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability to the active substances during long-term storage.

A further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Such a multiple unit tableted dosage form comprising enteric coating layered pellets of a proton pump inhibitor and antacid agent(s) also may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

Another object of the invention is to provide a tablet preparation comprising a proton pump inhibitor in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more antacid agent(s) in admixture with pharmaceutical excipients compressed onto the tablet core. The tablet core is enteric coating layered before the surrounding layer comprising the antacid agents is applied. Optionally a separating layer is applied on the tablet core before the core is enteric coating layered.

Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. One of the layers comprises the proton pump inhibitor in the form of enteric coating layered pellets in admixture with pharmaceutical excipients and the other layer(s) comprises(-e) the antacid agent(s)/alginate, respectively in admixture with pharmaceutical excipients. Optionally the two layers are separated by a separating layer to prevent tacking between the two layers.

The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible proton pump inhibitor, and antacid agent(s)/alginate.

Alternatively, the proton pump inhibitor in the form of enteric coating layered pellets may be mixed with an alginate and optionally pharmaceutical excipients to be administered in a sachet intended for oral administration after dispersion in a slightly acidic aqueous solution. The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form containing enteric coating layered units comprising the active substance being an acid susceptible proton pump inhibitor and granules comprising the other active substance(s), i.e. the antacid agent(s) as shown in Fig. 1.

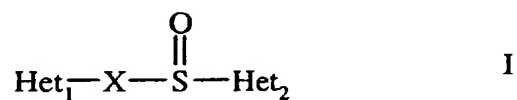
The antacid agent(s) may preferably be formulated in preparations intended for instant release. Alternatively, the components may be formulated in an effervescent formulation.

The different therapeutically active components used in the dosage forms are defined below.

Active substances

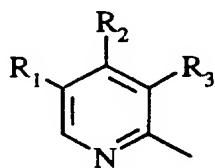
The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor.

5 Such proton pump inhibitors are for example compounds of the general formula I

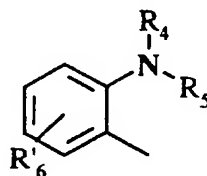


wherein

10 Het₁ is

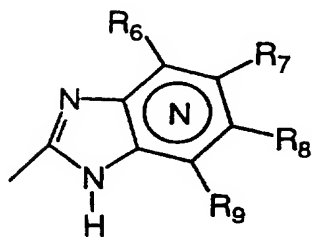


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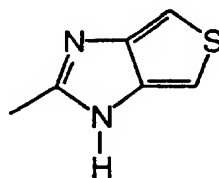


Het₂ is

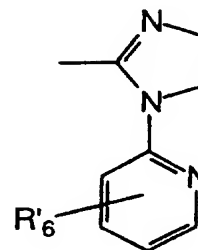
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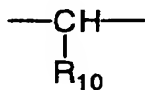
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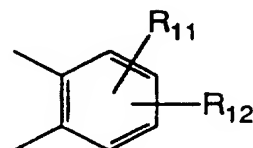
or



X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

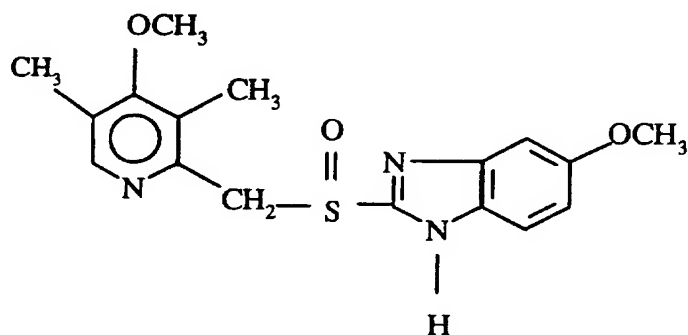
R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

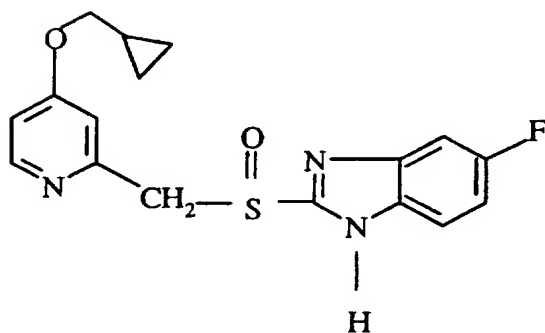
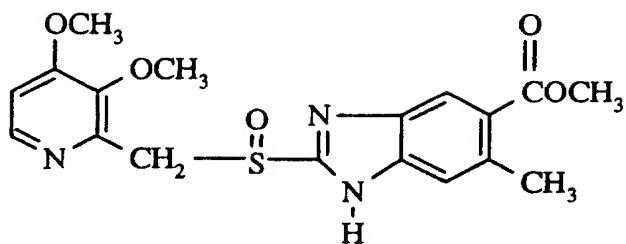
R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkylalkyl.

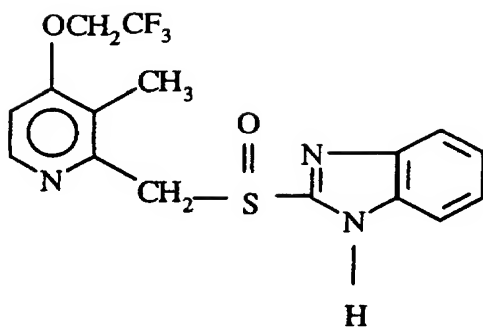
Examples of proton pump inhibitors according to formula I are



Omeprazole

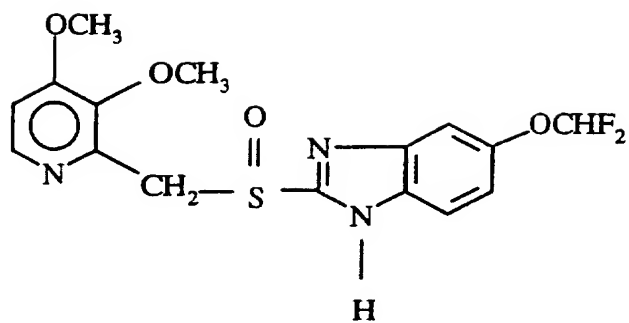


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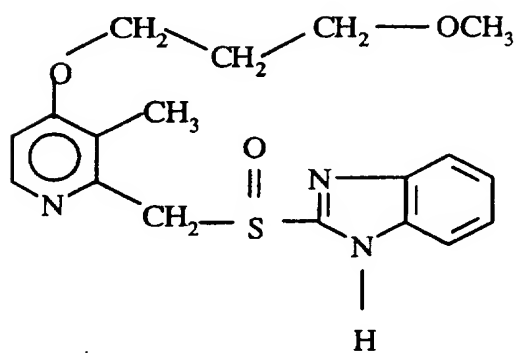


Lansoprazole

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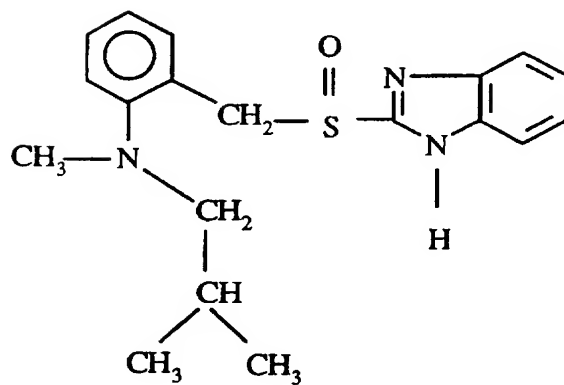


Pantoprazole

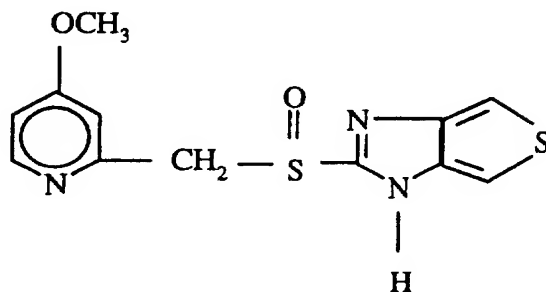


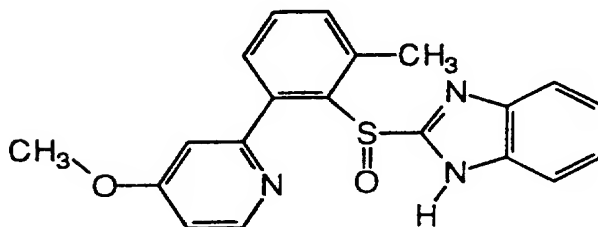
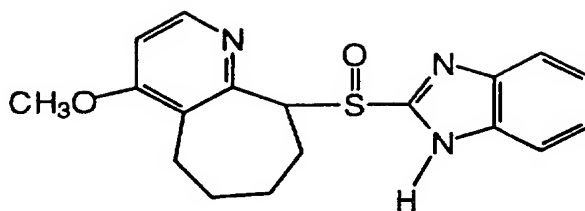
Pariprazole

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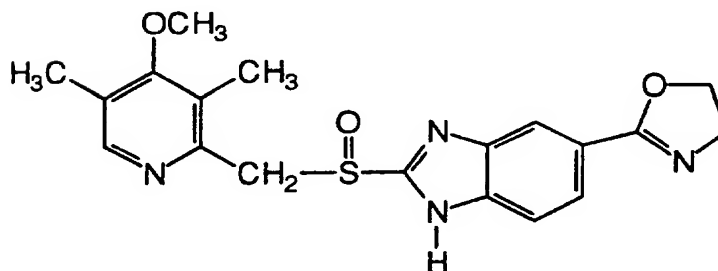
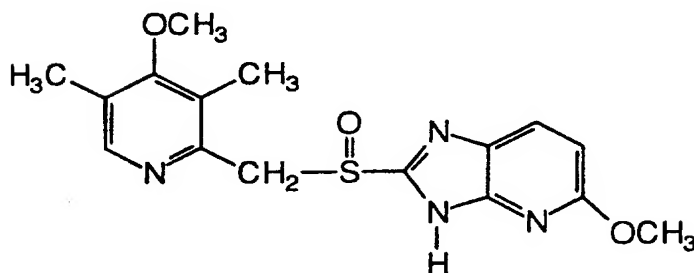


Leminoprazole





5



- 10 The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and
5 WO94/27988.

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor but H₂ receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/ 017080 or together
10 with antacid agent(s).

A wide variety of antacid agent(s) and/or alginates may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antacid agents include for example aluminium hydroxide, calcium
15 carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone or in combinations with each other. The alginates may be an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred antacid agents are magnesium or calcium based antacid agents and aluminium hydroxide/magnesium
20 carbonate complex. Suitable antacid agents are for instance described in US 5 409 709.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with antacid agent(s), is characterized in the following way. Individually enteric coating layered
25 units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antacid(s) and conventionally tablet excipients. The antacid(s) and tablet excipients may be dry mixed or wet-mixed into granules. The mixture of enteric coating layered units, antacid agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the

expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or

in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the proton pump inhibitor should be water soluble or rapidly disintegrating in water.

The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl

acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be
5 included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and
10 may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$,
15 $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other
20 compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

25 Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

The separating layer may also be used to separate two different layers of a tablet, as described in Fig. 2.

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively, the enteric coating layer described above may also be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with antacid granules and pharmaceutical excipients.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

The above described over-coating layer may also be used as a tablet filmcoating layer to obtain tablets of good appearance.

5 Antacid agent(s) or alginate preparation

The active substance in form of one or more antacid agent(s) are dry mixed with inactive excipients such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives. The mixture is wet massed with a granulation liquid. The wet mass is dried
10 preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients are for instance mannitol, corn starch, potato starch, low substituted hydroxypropylcellulose, microcrystalline cellulose and crosslinked polyvinylpyrrolidone. The dry mixture comprising antacid agent(s) is mixed with a suitable
15 granulation liquid comprising for instance hydroxypropylcellulose or polyvinylpyrrolidone dissolved in purified water or alcohol or a mixture thereof.

Alternatively, the antacid agent(s) are dry mixed with pharmaceutically acceptable excipients according to the above. The alginate preparation should also be prepared by dry
20 mixing with pharmaceutically acceptable excipients.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the
25 prepared antacid granules or with the prepared dry mixture comprising the antacid agent(s). The mixture is admixed with lubricant(s) and compressed into a multiple unit tableted dosage form. Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the
30 stability of the tablet during packaging and transport. Such a coating layer may further

comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

Further, the different active substances may be formulated into different layers, wherein the layer comprising the proton pump inhibitor preferably is in the form of a multiple unit
5 tableted dosage form layered with the prepared mixture of the antacid agent(s) or an alginate preparation. The two layers may be separated by a third layer comprising anti-tacking agents.

10 The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the total tablet weight and preferably less than 60 %. By increasing the amount of the granules comprising the antacid agent(s) and excipients, the fraction of enteric coating layered pellets of the proton pump inhibitor may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation according to the present
15 invention, the number of pellets in each tablet can be held high which in turn makes the tablet divisible with retained dosing accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing the acid susceptible proton pump inhibitor, optionally in admixture with
20 alkaline reacting compound(s), compressed into tablets together with the prepared antacid mixture and optionally tablet excipients. The addition of an alkaline reacting material to the proton pump inhibitor is not necessary, in any sense, but such a substance may further enhance the stability of the proton pump inhibitor or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating layer.

25 The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the tablet and they may also contain

one or more separating layer(s) in between the core material and the enteric coating layer(s).

Process

5

The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between the core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the antacid mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

15

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared antacid granules, tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the antacid or alginate preparation and finally compressed into a tablet. As a further alternative the proton pump inhibitor in form of a powder may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet core is then presscoated with the antacid preparation. Finally the tablet may be covered by a tablet coat.

25

As a further alternative, the proton pump inhibitor in the form of enteric coating layered pellets may be filled in a sachet together with an alginate optionally mixed with excipients.

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of dyspepsia and other gastrointestinal disorder to provide an immediate symptom relief and a long-lasting symptom resolution. The dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-1000 mg of the antacid agent(s)/alginate. Preferably, each dosage form will comprise 5-80 mg of the proton pump inhibitor and 100-900 mg of the antacid agent(s)/alginate, and more preferably 10-40 mg of proton pump inhibitor and 250 - 650 mg of the antacid agent(s)/alginate, respectively.

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 400 tablets).

Core material

Magnesium omeprazole	5.0	kg
Sugar sphere seeds	10.0	kg
Hydroxypropyl methylcellulose	0.75	kg
Water purified	20.7	kg

Separating layer

	Core material (acc. to above)	10.2	kg
	Hydroxypropyl cellulose	1.02	kg
	Talc	1.75	kg
5	Magnesium stearate	0.146	kg
	Water purified	21.4	kg

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	11.9	kg
10	Methacrylic acid copolymer (30 % suspension)	19.8	kg
	Triethyl citrate	1.79	kg
	Mono- and diglycerides (NF)	0.297	kg
	Polysorbate 80	0.03	kg
	Water purified	11.64	kg

15

Over-coating layer

	Enteric coating layered pellets (acc. to above)	20.0	kg
	Hydroxypropyl methylcellulose	0.238	kg
	Magnesium stearate	0.007	kg
20	Water purified	6.56	kg

Tablets

	Prepared pellets comprising omeprazole Mg-salt (acc. to above)	31.3	g
	Microcrystalline cellulose	140.0	g
25	Calcium carbonate	100.0	g
	Aluminium hydroxide/magnesium carbonate	100.0	g
	Potato starch	46.4	g
	Water purified	314	g
	Polyvidone crosslinked	38.0	g
30	Sodium stearyl fumarate	4.6	g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

5

The prepared core material was covered with a separating layer of a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed
10 apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose containing magnesium stearate. The over-coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in purified hot water to form the
15 granulation liquid. Calcium carbonate, aluminium hydroxide/magnesium carbonate, potato starch and microcrystalline cellulose are dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 50°C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

20 The enteric coating layered pellets with an over-coating layer, prepared granules, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 110N.

25

Optionally the obtained tablets were covered with a tablet coating layer.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	93%

5 Example 2:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 500 tablets).

10 Core material

Magnesium omeprazole	10.0 kg
Sugar sphere seeds	10.0 kg
Hydroxypropyl methylcellulose	1.5 kg
Water purified	29.9 kg

15

Separating layer

Core material (acc. to above)	20.0 kg
Hydroxypropyl cellulose	2.0 kg
Talc	3.43 kg
Magnesium stearate	0.287 kg
Water purified	41.0 kg

20

Enteric coating layer

Pellets covered with separating layer (acc. to above)	24.5 kg
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	Methacrylic acid copolymer (30 % suspension)	32.7 kg
	Triethyl citrate	2.94 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.049 kg
5	Water purified	19.19 kg

Over-coating layer

	Enteric coating layered pellets (acc. to above)	37.8 kg
	Hydroxypropyl methylcellulose	0.49 kg
10	Magnesium stearate	0.0245 kg
	Water purified	11.6 kg

Tablets

	Prepared pellets comprising magnesium omeprazole (acc. to above)	47.45 g
15	Calcium carbonate	123.9 g
	Magnesium hydroxide	123.9 g
	Potato starch	52.2 g
	Water purified	435 g
	Microcrystalline cellulose	175 g
20	Polyvidone crosslinked	50 g
	Sodium stearyl fumarate	6.0 g

Enteric coating layered pellets of magnesium omeprazole with an overcoating layer were prepared as in Example 1.

25

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled

30 through sieve 1 mm in an oscillating mill equipment.

The enteric coated layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30-40N.

Optionally the obtained tablets were covered with a tablet coating layer.

10 Example 3:

Multiple unit tableted dosage form comprising S-omeprazole magnesium salt and antacid agents (batch size 500 tablets).

15 Core material

S-omeprazole magnesium salt	120 g
Sugar sphere seeds	150 g
Hydroxypropyl methylcellulose	18 g
Polysorbate 80	2.4 g
20 Water purified	562 g

Separating layer

Core material (acc. to above)	200 g
Hydroxypropyl cellulose	30 g
25 Talc	51.4 g
Magnesium stearate	4.3 g
Water purified	600 g

Enteric coating layer

30 Pellets covered with separating layer (acc.to above)	250 g
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	Methacrylic acid copolymer (30% suspension)	333.7 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
5	Water purified	196 g

Tablets

	Prepared pellets comprising (s)-omeprazole Mg-salt	63.7 g
	Calcium carbonate	123.9 g
10	Magnesium hydroxide	123.9 g
	Potato starch	52.2 g
	Water purified	435 g
	Microcrystalline cellulose	175 g
	Polyvidone crosslinked	50.0 g
15	Sodium stearyl fumarate	6.0 g

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder and polysorbate 80. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed.

The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets, prepared granules, polyvidone crosslinked, microcrystalline cellulose and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30N.

Optionally the obtained tablets were covered with a tablet coating layer.

Exampel 4:

Three-layered tableted dosage form with a fast disintegrating layer comprising omeprazole, a separating layer and a layer comprising alginic acid. (batch size 1 000 tablets)

Tablets

First tablet layer

Alginic acid	500 g
Sodium hydrogencarbonate	150 g
Microcrystalline cellulose	87 g
Polyvinyl pyrrolidone crosslinked	13 g
Sodium stearyl fumarate	3.8 g

25

Separating layer

Microcrystalline cellulose	80 g
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Second tablet layer

Enteric coating layered pellets comprising omeprazole Mg-salt	78.3 g
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30

(manufacturing and composition as in example 1)

Microcrystalline cellulose	174 g
Polyvinyl pyrrolidone crosslinked	26 g
Sodium stearyl fumarate	1.4 g

5

Alginic acid, sodium hydrogencarbonate, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and precompressed as a first layer in a tableting machine equipped with 10x21 mm oval punches. Microcrystalline cellulose was filled on top of the first layer to form a separating layer to the next layer.

10

The enteric coating layered pellets, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and filled on top of the separating layer. The three layers were compressed into a three layers tablet.

15 Optionally the tablet was covered by a tablet coating layer.

The amount of omeprazole in each tablet is approx. 10 mg and the amount of alginic acid was approx 500 mg.

20 The best mode to practise the invention is described in Examples 1 and 4.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

25 Example 5

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
5	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
	Water purified	802 g

Separating layer

10	Core material	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

Enteric coating layer

15	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
20	Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-
 25 mixed. The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

5

Example 6

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

10 Core material

Magnesium omeprazole	1 500 g
Sugar sphere seeds	1 500 g
Hydroxypropyl methylcellulose	420 g
Aerosil®	8 g
15 Water purified	4 230 g

Separating layer

Core material	500 g
Hydroxypropyl cellulose	40 g
20 Talc 67 g	
Magnesium stearate	6 g
Water purified	800 g

Enteric coating layer

25 Pellets covered with separating layer	500 g
Methacrylic acid copolymer	200 g
Triethyl citrate	60 g
Water purified	392 g

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

5

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 7

10

Preparation of enteric coating layered pellets with cores of silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
15	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulphate	0.08 kg
	Water purified	28.00 kg

20 Separating layer

	Core material (acc. to above)	10.00 kg
	Hydroxypropyl methylcellulose	0.80 kg
	Water purified	10.00 kg

25 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides (NF)	3 g
30	Polysorbate 80	1 g

Water purified

463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed onto the pellets covered with separating layer in a fluid bed apparatus.

Example 8

Preparation of enteric coating layered pellets.

Enteric coating layer

Pellets covered with separating layer

(manufacturing and composition

as in example 10)

500 g

Methacrylic acid copolymer

250 g

Polyethylene glycol 6000

75 g

Mono- and diglycerides (NF)

12.5 g

Polysorbate 80

1.2 g

Water purified

490 g

Example 9

Preparation of enteric coating layered pellets.

Enteric coating

	Pellets covered with separating layer	500 g
	(manufacturing and composition as in example 1)	
	Hydroxypropyl methylcellulose phthalate	250 g
5	Cetanol	50 g
	Ethanol (95%)	1000 g
	Acetone	2500 g

Example 10

10

Preparation of enteric coating layered pellets.

Core material

	Omeprazole	225 g
15	Mannitol	1425 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
	Lactose anhydrous	80 g
	Sodium lauryl sulphate	5 g
20	Disodium hydrogen phosphate dihydrate	8 g
	Water purified	350 g

Separating layer

	Core material	300 g
25	Hydroxypropyl cellulose	30 g
	Talc	51 g
	Magnesium stearate	4 g

Enteric coating layer

30	Pellets covered with separating layer	300 g
----	---------------------------------------	-------

Methacrylic acid copolymer	140	g
Triethyl citrate	42	g
Mono- and diglycerides (NF)	7	g
Polysorbate 80	0.7	g

5

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

10

Preparation of active substance.

15

Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with one or more antacid agents or alginates and optionally
5 pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components and wherein the proton pump inhibitor is protected by an enteric coating layer.
2. A dosage form according to claim 1, wherein the dosage form is a tablet
10 formulation.
3. A dosage form according to claim 1, wherein the dosage form is a sachet formulation.
- 15 4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
5. A dosage form according to claim 1, wherein the dosage form comprises an acid
20 susceptible proton pump inhibitor and two antacid agents.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, one of its single enantiomers or an alkaline salt thereof.
- 25 7. A dosage form according to claim 6, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its single enantiomers or an alkaline salt thereof.

9. A dosage form according to one of claims 6 - 8, wherein the antacid agents are aluminium hydroxide in combination with magnesium carbonate.

10. A dosage form according to any of claims 6 - 8, wherein the antacid agents are
5 magnesium hydroxide in combination with calcium carbonate.

11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 5-80 mg and the amount of antacid/alginate is in the range of 100-900 mg.

10 12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of antacid/alginate is in the range of 250-650 mg.

13. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers optionally separated by a separating layer, and one layer comprising a
15 proton pump inhibitor and the other layer comprising one or more antacid agents or alginates.

14. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in
20 the form of enteric coating layered pellets compressed together with a antacid preparation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antacid preparation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.

25

15. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

16. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.
- 5 17. A tableted dosage form according to claim 14, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.
18. A tableted dosage form according to claim 14, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically
10 acceptable excipients.
19. A tableted dosage form according to claim 14, wherein the tablet is divisible.
20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to an
15 aqueous suspension comprising antacid agent(s) and enteric coating layered pellets of a proton pump inhibitor.
21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising the proton pump inhibitor surrounded by a layer comprising the
20 antacid preparation.
22. A tableted dosage form according to claim 14, wherein the proton pump inhibitor is in the form of a multiple unit tableted dosage form surrounded with a separate layer comprising the antacid agent(s) or an alginate preparation.
- 25 23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor in one layer and one or more antacid agents or an alginate in another layer, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets, the pellets are mixed with pharmaceutically acceptable excipients

and precompressed and further layered with a surrounding layer of an antacid or an alginate preparation and finally compressed into a tablet.

24. A process for the manufacture of a fixed dosage form comprising an acid susceptible
5 proton pump inhibitor and one or more antacid agents in a multiple unit tableted dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with an antacid preparation and optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid
10 resistance of the enteric coating layer.

25. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agent(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with tablet excipients and
15 compressed into a tablet, which tablet is covered with an enteric coating layer and optionally a separating layer has applied onto the tablet before the enteric coating layer, the antacid agent(s) mixed with pharmaceutically acceptable excipients are thereafter compressed onto the enteric coating layered tablet.

20 26. A method for the treatment of disorders associated with dyspepsia in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tableted dosage form according to any of claims 1 to 22.

27. A method according to claim 26, wherein the disorder is a gastric disorder
25 associated with heartburn.

28. Use of a dosage form according to any of claims 1 to 22 for the manufacture of a medicament for the treatment of disorders associated with dyspepsia.

29. Use according to claim 28, wherein the disorder is a gastric disorder associated with heartburn.

1 / 1

Fig. 1

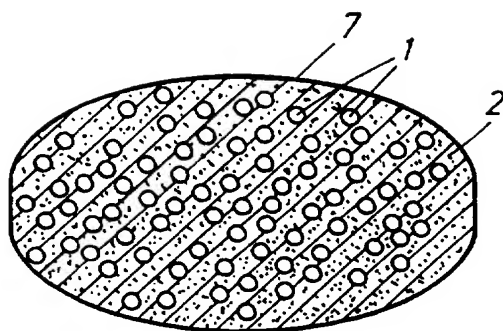


Fig. 2

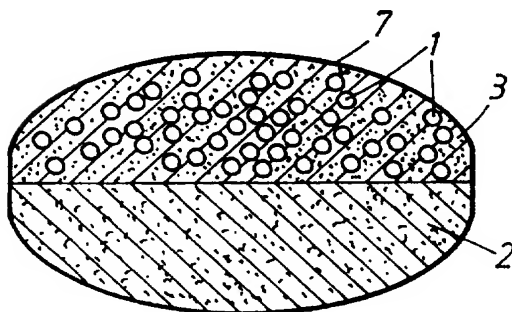
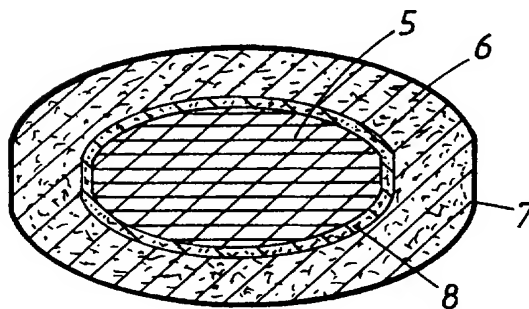


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01737

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 33/08, A61K 33/10, A61K 9/20, A61K 9/26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, WPI, WPIL, CLAIMS, CA PLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0338861 A2 (WALTON S.A.), 25 October 1989 (25.10.89), column 1, line 52 - column 2, line 14; column 2, line 15 - line 22; column 3, line 52 - line 57, figures 7-8 --	1-29
X	US 5244670 A (J.G. UPSON ET AL), 14 Sept 1993 (14.09.93), column 1, line 59 - line 68; column 2, line 43 - line 55 --	1-29
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 4, line 25 - page 5, line 2; page 8, line 22 - line 32 --	14-29

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 April 1997

Date of mailing of the international search report

22 -04- 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01737

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90), page 3, line 41 - line 46; page 4, line 42 - line 57 --	14-29
A	STN International, File CAPLUS, CAPLUS accession no. 1989:490176, K. Takeuchi et al: "Healing process of duodenal ulcers induced by indomethacin plus histamine in rats", Digestion (1989), 42(4), 202-11 -- -----	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01737

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 26-27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 26-27 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

04/03/97

PCT/SE 96/01737

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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01737

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**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation ⁵ : A61K 31/44		A1	(11) Internationale Veröffentlichungsnummer: WO 92/04898 (43) Internationales Veröffentlichungsdatum: 2. April 1992 (02.04.92)
(21) Internationales Aktenzeichen: PCT/EP91/01689 (22) Internationales Anmeldedatum: 6. September 1991 (06.09.91) (30) Prioritätsdaten: 2993/90-9 14. September 1990 (14.09.90) CH 2226/91-6 25. Juli 1991 (25.07.91) CH (71) Anmelder (für alle Bestimmungsstaaten ausser US): BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Str. 2, Postfach 100310, D-7750 Konstanz (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US) : KLEMM, Kurt [DE/DE]; Im Weinberg 2, D-7753 Allensbach (DE). KRÜGER, Uwe [DE/DE]; Neuhauser Str. 11, D-7750 Konstanz (DE).		(72) Erfinder (für alle Bestimmungsstaaten ausser CA US): STURM, Ernst ; Bohlstraße 9, D-7750 Konstanz 18 (DE). SENN-BILFINGER, Jörg ; Sântisstraße 7, D-7750 Konstanz (DE). (74) Gemeinsamer Vertreter: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Postfach 10 03 10, Byk-Gulden-Str. 2, D-7750 Konstanz (DE). (81) Bestimmungsstaaten: AT (europäisches Patent), AU, BE (europäisches Patent), CA, CH (europäisches Patent), CS, DE, DE (europäisches Patent), DK (europäisches Patent), ES (europäisches Patent), FI, FR (europäisches Patent), GB (europäisches Patent), GR (europäisches Patent), HU, IT (europäisches Patent), JP, KR, LU (europäisches Patent), NL (europäisches Patent), NO, PL, SE (europäisches Patent), SU ⁺ , US. Veröffentlicht Mit internationalem Recherchenbericht.	
(54) Title: USE OF PYRIDYLMETHYLSULPHINYL-1H-BENZIMIDAZOLE DERIVATES IN THE TREATMENT OF ILLNESSES CAUSED BY HELICOBACTER BACTERIA (54) Bezeichnung: VERWENDUNG VON PYRIDYLMETHYLSULFINYL-1H-BENZIMIDAZOL DERIVATEN ZUR BEHANDLUNG DURCH HELICOBACTER VERURSACHTEN ERKRANKUNGEN			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract The invention concerns the use of compound of formula (I), in which the substituents and symbols are as defined in the specification, against <i>Helicobacter</i> bacteria.			
(57) Zusammenfassung Die Verwendung von Verbindungen der Formel (I), worin die Substituenten und Symbole die in der Beschreibung genannten Bedeutungen haben, für die Bekämpfung von <i>Helicobacter</i> -Bakterien wird beschrieben.			

+ BESTIMMUNGEN DER "SU"

Die Bestimmung der "SU" hat Wirkung in der Russischen Föderation. Es ist noch nicht bekannt, ob solche Bestimmungen in anderen Staaten der ehemaligen Sowjetunion Wirkung haben.

LEDIGLICH ZUR INFORMATION

Code, die zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AT	Österreich	ES	Spanien	ML	Mali
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DK	Dänemark	MG	Madagaskar		

**VERWENDUNG VON PYRIDYLMETHYLSULFINYL-1H-BENZIMIDAZOL DERIVATEN
ZUR BEHANDLUNG DURCH HELICOBACTER VERURSACHTEN ERKRANKUNGEN**

Anwendungsgebiet der Erfindung

Die Erfindung betrifft neue orale Arzneiformen. Die neuen Arzneiformen werden zur Behandlung von Erkrankungen des Magens und/oder Darms eingesetzt, die durch Helicobacter-Bakterien hervorgerufen werden.

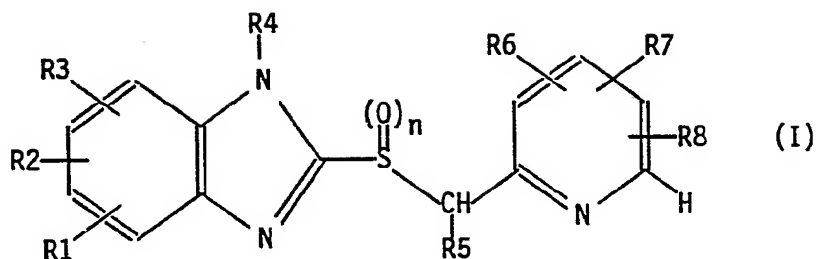
Stand der Technik

In einer Vielzahl von Patentanmeldungen und Patenten werden Pyridylmethylsulfinyl-1H-benzimidazole beschrieben, die magensäuresektionshemmende Eigenschaften besitzen. Im Zusammenhang mit der vorliegenden Erfindung seien hier insbesondere die folgenden Patentanmeldungen und Patente erwähnt: EP-A-134 400 (= USP 4,555,518), EP-A-127 763 (= USP 4,560,693), EP-B-166 287 (= USP 4,758,579), EP-A-201 575 (= USP 4,686,230), W089/05299 und W089/11479. - In der europäischen Patentanmeldung EP-A-382 489 wird die Eignung bestimmter Pyridylmethylsulfinyl-1H-benzimidazole, die im Benzimidazolteil gewünschtenfalls durch Methoxy oder Trifluormethyl substituiert sind, zur Behandlung infektiöser Erkrankungen, die durch Bakterien vom Stamme Campylobacter (= Helicobacter) hervorgerufen werden, beschrieben und beansprucht. In der internationalen Patentanmeldung W090/09175 wird die Verwendung von Omeprazol bei der Behandlung von infektiösen, insbesondere durch Campylobacter pylori hervorgerufenen Erkrankungen offenbart. - Aufgrund der geringen Stabilität und leichten Säurezersetzlichkeit der Pyridylmethylsulfinyl-1H-benzimidazole wird in verschiedenen Patentanmeldungen (z.B. EP-A-244 380 oder EP-A-247 983) auf die Notwendigkeit verwiesen, bei oraler Applikation diese Wirkstoffe in einer magensaftresistenten Form zu verabreichen. Auch in der obengenannten EP-A-382 489 wird als orale Darreichungsform für die Campylobacter-Bekämpfung beispielhaft eine "enteric coated" Formulierung verwendet.

Beschreibung der Erfindung

Gegenstand der Erfindung ist die Verwendung von Verbindungen der Formel I

-2-



worin

- R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
- R2 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
- R3 ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
- R4 Wasserstoff oder eine unter physiologischen Bedingungen leicht abspaltbare Gruppe bedeutet,
- R5 Wasserstoff oder 1-4C-Alkyl bedeutet,
- R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
- R7 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
- R8 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet und
- n die Zahl 0 oder 1 darstellt,

und ihren pharmakologisch verträglichen Salzen zur Herstellung von oral zu verabreichenden Arzneimitteln für die Bekämpfung von Helicobacter-Bakterien.

1-4C-Alkyl steht für geradkettige oder verzweigte Alkylreste; beispielsweise seien der Butyl-, i-Butyl-, sec.-Butyl-, t-Butyl-, Propyl-, Isopropyl-, Ethyl- und insbesondere der Methylrest genannt.

1-4C-Alkoxy steht für geradkettige oder verzweigte Alkoxyreste; beispielsweise seien genannt der Butoxy-, i-Butoxy-, sec.-Butoxy-, t-Butoxy-, Propoxy-, Isopropoxy-, Ethoxy- und insbesondere der Methoxyrest.

Als ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy seien beispielsweise der 1,2,2-Trifluorethoxy-, der 2,2,3,3,3-Pentafluorpropoxy-, der Perfluorethoxy- und insbesondere der 1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, der 2,2,2-Trifluorethoxy- und der Difluormethoxyrest genannt.

Als ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy seien beispielsweise der 1,1-Difluorethylendioxy- ($-O-CF_2-CH_2-O-$), der 1,1,2,2-Tetrafluorethylendioxy- ($-O-CF_2-CF_2-O-$) und insbesondere der Difluormethylendioxy- ($-O-CF_2-O-$) und der 1,1,2-Trifluorethylendioxyrest ($-O-CF_2-CHF-O-$) genannt.

Wenn R2 und R3 gemeinsam ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeuten, so sind die Substituenten R2 und R3 in Nachbarpositionen am Benzoteil des Benzimidazolringes gebunden.

Eine unter physiologischen Bedingungen leicht abspaltbare Gruppe R4 ist ein Substituent, der durch - gegebenenfalls enzymatisch katalysierte - Hydrolyse vom Stickstoffatom unter Ausbildung einer N-H-Bindung abgetrennt wird, wobei er selbst - unter Anbindung einer Hydroxylgruppe - in eine physiologisch unbedenkliche und insbesondere pharmakologisch verträgliche Verbindung umgewandelt wird. Als abspaltbare Gruppen R4 seien insbesondere alle Arten von substituierten Carbonylgruppen genannt, wie die Alkylcarbonyl-, Arylcarbonyl-, Aralkylcarbonyl-, Alkoxycarbonyl-, Aryloxycarbonyl-, Aralkoxycarbonyl- oder die gegebenenfalls substituierte Carbamoylgruppe. Beispielsweise seien die Methoxycarbonyl-, t-Butoxycarbonyl-, Benzoyl-, Phenylcarbamoyl- und die Dimethylcarbamoylgruppe genannt.

Als Salze kommen für Verbindungen der Formel I, in denen n die Zahl 0 bedeutet (Sulfide), bevorzugt alle pharmakologisch verträglichen Säureadditionssalze in Betracht. Besonders erwähnt seien die pharmakologisch verträglichen Salze der in der Galenik üblicherweise verwendeten anorganischen und organischen Säuren. Als solche eignen sich beispielsweise wasserlösliche und wasserunlösliche Säureadditionssalze, wie das Hydrochlorid, Hydrobromid, Hydroiodid, Phosphat, Nitrat, Sulfat, Acetat, Citrat, Gluconat, Benzoat, Hibenzoat, Fendizoat, Butyrat, Sulfosalicylat, Maleat, Laurat, Malat, Fumarat, Succinat, Oxalat, Tartrat, Amsonat, Embonat, Metembonat, Stearat, Tosilat, 2-Hydroxy-3-naphthoat, 3-Hydroxy-2-naphthoat oder Mesilat.

Für Verbindungen der Formel I, in denen n die Zahl 1 bedeutet (Sulfoxide), kommen als Salze bevorzugt pharmakologisch verträgliche basische Salze in Betracht, insbesondere pharmakologisch verträgliche Salze mit in der Galenik üblicherweise verwendeten anorganischen und organischen Basen. Als Beispiele für basische Salze seien Lithium-, Natrium-, Kalium-, Calcium-, Aluminium-, Magnesium-, Titan-, Ammonium- oder Guanidiniumsalze erwähnt.

Von den Helicobacter-Stämmen, gegenüber denen sich die Verbindungen der Formel I als wirksam erweisen, sei insbesondere der Stamm Helicobacter pylori erwähnt.

Als oral zu verabreichende Arzneimittel seien beispielsweise Tabletten, Dragees, harte und weiche Kapseln, z.B. aus Gelatine, dispergierbare Pulver, Granulate, wäßrige und ölige Suspensionen, Emulsionen, Lösungen oder Sirupe erwähnt, wobei die Tabletten, Dragees, Kapseln oder Granulate vorteilhafterweise so beschaffen sind, daß sie sich im Magensaft leicht auflösen und den Wirkstoff im Magen freigeben.

Zur kombinierten Behandlung von Magenerkrankungen, die sowohl auf einer erhöhten Magensäuresekretion, als auch auf einer Schädigung des Magens durch Helicobacter pylori beruhen, seien auch solche oral zu verabreichenden Arzneiformulierungen erwähnt, die in einer Einzeldosis Wirkstoffe der Formel I gleichzeitig sowohl in magensaftresistenter, als auch in nicht magensaftresistenter Form enthalten. Beispielsweise seien genannt Tabletten, die den Wirkstoff sowohl in einem magensaftresistenten Kern, als auch in einer nicht magensaftresistenten Hülle enthalten, oder Kapseln, die mit magensaftresistenten und nicht magensaftresistenten Pellets oder (Mini)tabletten gefüllt sind.

Im allgemeinen werden in der Humanmedizin die Wirkstoffe in einer Tagesdosis von etwa 0,05 bis etwa 5, vorzugsweise 0,1 bis 2,5 mg/kg Körpergewicht, gegebenenfalls in Form mehrerer, vorzugsweise 2 bis 6 Einzelgaben zur Erzielung des gewünschten Ergebnisses verabreicht.

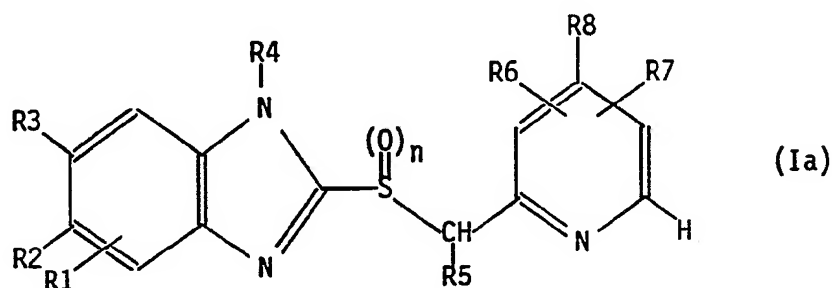
Sollen die Verbindungen der Formel I und/oder ihr Salze zur Behandlung von Erkrankungen des Magens, die auf der Anwesenheit von Helicobacter pylori beruhen, eingesetzt werden, so können die zu verabreichenden Arzneimittel auch einen oder mehrere pharmakologisch aktive Bestandteile anderer Arzneimittelgruppen enthalten. Hervorzuheben ist in diesem Zusammenhang insbesondere die Kombination von Verbindungen der Formel I und/oder ihren Salzen mit antimikrobiellen,

gegen *Helicobacter pylori* wirksame Substanzen, wie beispielsweise Penicillin G, Gentamycin, Erythromycin, Nitrofurazon, Nitrofurantoin, Furazolidon, Metronidazol und insbesondere Amoxycillin, mit dem Ziel, die Hauptwirkung in überadditivem Sinn zu verstärken. Besonders bevorzugt und daher weiterer Gegenstand der Erfindung ist in diesem Zusammenhang die Kombination des Wirkstoffes 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol [= Pantoprazol (INN)] und seiner Salze mit antimikrobiell wirksamen Substanzen, insbesondere mit Amoxycillin.

Überraschenderweise wurde gefunden, daß die Verbindungen der Formel I in saurem Milieu gegen *Helicobacter*-Bakterien wesentlich wirksamer sind als in neutralem Milieu, und daß sie demzufolge - entgegen der aus dem Stand der Technik zu entnehmenden Lehre - sinnvollerweise nicht in einer magensaftresistenten Form verabreicht werden sollten.

Bevorzugter Gegenstand der Erfindung ist somit die Verwendung von Verbindungen der Formel I und ihren pharmakologisch verträglichen Salzen zur Herstellung von oral zu verabreichenden, nicht magensaftresistent formulierten Arzneimitteln für die Bekämpfung von *Helicobacter*-Bakterien.

Eine erwähnenswerte Ausgestaltung der Erfindung (Ausgestaltung a) ist die erfindungsgemäße Verwendung von Verbindungen der Formel Ia,



worin

R1 Wasserstoff oder Methyl bedeutet,

R2 Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 Difluormethylenedioxy, 1,1,2-Trifluorethylenedioxy oder 1-Chlor-1,2,2-trifluorethylenedioxy bedeutet,

- R3 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 Difluormethylenedioxy, 1,1,2-Trifluorethylenedioxy oder 1-Chlor-1,2,2-trifluorethylenedioxy bedeutet,
- R4 Wasserstoff bedeutet,
- R5 Wasserstoff, Methyl oder Ethyl bedeutet,
- R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
- R7 Wasserstoff oder 1-4C-Alkyl bedeutet,
- R8 1-4C-Alkoxy bedeutet und
n die Zahl 0 oder 1 darstellt,
und ihren pharmakologisch verträglichen Salzen.

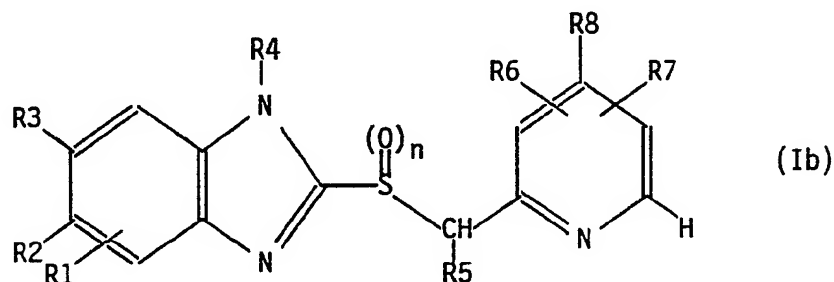
Besonders erwähnenswert ist die erfindungsgemäße Verwendung der folgenden Verbindungen der Ausgestaltung a und ihrer pharmakologisch verträglichen Salze:

- 2-[(4-Methoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4-Methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,

2,2-Difluor-6-[(4-methoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,
2,2-Difluor-6-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2,2-Difluor-6-[(4-methoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
5-Difluormethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-4,6-dimethyl-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-1H-benzimidazol,
5-(1,1,2,2-Tetrafluorethoxy)-2-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-1H-benzimidazol,
2,2-Difluor-6-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,
5-(2-Chlor-1,1,2-trifluorethoxy)-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-(2-Chlor-1,1,2-trifluorethoxy)-2-{[1-(4-methoxy-2-pyridyl)ethyl]-sulfinyl}-1H-benzimidazol,
5-(2-Chlor-1,1,2-trifluorethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazol.
2[(4-Methoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-5-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4-Methoxy-3,5-dimethyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4-Methoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,

5-Difluormethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)-methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4-methoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4-methoxy-2-pyridyl)methylthio]-1H-benzimidazol,
2,2-Difluor-6-[(4-methoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2,2-Difluor-6-[(4-methoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
5-Difluormethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylthio]-4,6-dimethyl-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-1H-benzimidazol,
5-(1,1,2,2-Tetrafluorethoxy)-2-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-1H-benzimidazol,
2,2-Difluor-6-{[1-(4-methoxy-2-pyridyl)ethyl]sulfinyl}-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,
5-(2-Chlor-1,1,2-trifluorethoxy)-2-[(4-methoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-(2-Chlor-1,1,1-trifluorethoxy)-2-{[1-(4-methoxy-2-pyridyl)ethyl]-sulfinyl}-1H-benzimidazol,
5-(2-Chlor-1,1,2-trifluorethoxy)-2-[(4-methoxy-3-methyl-2-pyridyl)-methylthio]-1H-benzimidazol.

Eine weitere erwähnenswerte Ausgestaltung der Erfindung (Ausgestaltung b) ist die erfindungsgemäße Verwendung von Verbindungen der Formel Ib,



worin

- R1 Wasserstoff oder Methyl bedeutet,
 R2 Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
 R3 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
 R4 Wasserstoff bedeutet,
 R5 Wasserstoff, Methyl oder Ethyl bedeutet,
 R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
 R7 1-4C-Alkoxy bedeutet,
 R8 1-4C-Alkoxy bedeutet und
 n die Zahl 0 oder 1 darstellt,
 und ihren pharmakologisch verträglichen Salzen.

Besonders erwähnenswert ist die erfindungsgemäße Verwendung der folgenden Verbindungen der Ausgestaltung b und ihrer pharmakologisch verträglichen Salze:

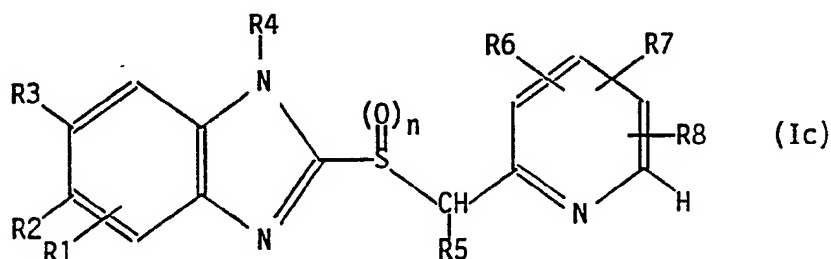
- 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-4,6-dimethyl-1H-benzimidazol,
 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
 5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,

2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazol,
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol.
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-4,6-dimethyl-1H-benzimidazol,
5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,

2[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,

2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol.

Eine weitere erwähnenswerte Ausgestaltung der Erfindung (Ausgestaltung c) ist die erfindungsgemäße Verwendung von Verbindungen der Formel Ic,



worin

R1 Wasserstoff bedeutet,

R2 Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,

R3 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,

R4 Wasserstoff bedeutet,

R5 Wasserstoff, Methyl oder Ethyl bedeutet,

R6 Wasserstoff oder 1-4C-Alkyl bedeutet,

R7 1-4C-Alkoxy bedeutet,

R8 Benzyloxy bedeutet und

n die Zahl 0 oder 1 darstellt,

und ihren pharmakologisch verträglichen Salzen.

Besonders erwähnenswert ist die erfindungsgemäße Verwendung der folgenden Verbindungen der Ausgestaltung c und ihrer pharmakologisch verträglichen Salze:

2,2-Difluor-6-[(5-benzyloxy-4-methoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

2-[(4-Benzyloxy-3-methoxy-2-pyridyl)methylsulfinyl]-5-difluormethoxy-1H-benzimidazol,

2-[(3-Benzyloxy-4-methoxy-2-pyridyl)methylsulfinyl]-5-difluormethoxy-1H-benzimidazol,

2-[(5-Benzyloxy-4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-difluormethoxy-1H-benzimidazol,

2-[(5-Benzyloxy-4-methoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,

2,2-Difluor-6-[(5-benzyloxy-4-methoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

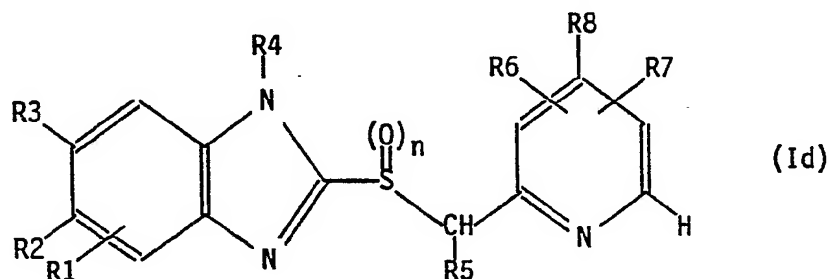
2-[(4-Benzyloxy-3-methoxy-2-pyridyl)methylthio]-5-difluormethoxy-1H-benzimidazol,

2-[(3-Benzyloxy-4-methoxy-2-pyridyl)methylthio]-5-difluormethoxy-1H-benzimidazol,

2-[(5-Benzyloxy-4-methoxy-3-methyl-2-pyridyl)methylthio]-5-difluormethoxy-1H-benzimidazol,

2-[(5-Benzyloxy-4-methoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol.

Eine weitere erwähnenswerte Ausgestaltung der Erfindung (Ausgestaltung d) ist die erfindungsgemäße Verwendung von Verbindungen der Formel Id,



worin

R1 Wasserstoff bedeutet,

-13-

- R2 Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
- R3 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
- R4 Wasserstoff bedeutet,
- R5 Wasserstoff; Methyl oder Ethyl bedeutet,
- R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
- R7 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
- R8 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy oder Difluormethoxy bedeutet und
- n die Zahl 0 oder 1 darstellt,
- und ihren pharmakologisch verträglichen Salzen.

Besonders erwähnenswert ist die erfindungsgemäße Verwendung der folgenden Verbindungen der Ausgestaltung d und ihrer pharmakologisch verträglichen Salze:

- 5-Difluormethoxy-2-{[3-methoxy-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylsulfinyl}-1H-benzimidazol,
- 5-Difluormethoxy-2-{[3-methyl-4-(2,2,2-trifluorethoxy)-pyridyl]methylsulfinyl}-1H-benzimidazol,
- 2-{[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylsulfinyl}-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
- 2,2-Difluor-6-{[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylsulfinyl}-5H-[1,3]-dioxolo[4,5-f]benzimidazol.
- 5-Difluormethoxy-2-{[3-methoxy-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylthio}-1H-benzimidazol,
- 5-Difluormethoxy-2-{[3-methyl-4-(2,2,2-trifluorethoxy)-pyridyl]methylthio}-1H-benzimidazol,
- 2-{[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylthio}-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
- 2,2-Difluor-6-{[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methylthio}-5H-[1,3]-dioxolo[4,5-f]benzimidazol.

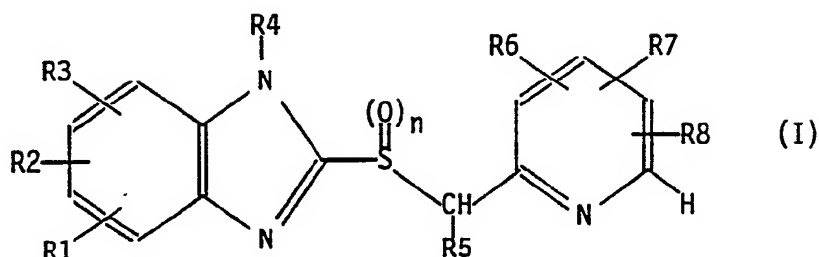
Die Verbindungen der Formel I und ihre pharmakologisch verträglichen Salze sind aus den folgenden Patentanmeldungen und Patenten bekannt: EP-A-134 400 (= USP 4,555,518), EP-A-127 763 (= USP 4,560,693), EP-B-166 287 (= USP 4,758,579), EP-A-201 575 (= USP 4,686,230), W089/05299 und W089/11479.

Die Herstellung der oral zu verabreichenden Arzneimittel unter Verwendung der Wirkstoffe der Formel I erfolgt in einer dem Fachmann an sich bekannten Weise.

Sollen die Verbindungen der Formel I mit antimikrobiellen, gegen *Helicobacter pylori* wirksamen Substanzen kombiniert werden, so werden die antimikrobiell wirksamen Substanzen in einer dem Fachmann bekannten Dosierung verabfolgt. Die Verbindungen der Formel I werden vorteilhafterweise in einer höheren Dosierung verabfolgt, als diese zur Erlangung einer therapeutisch erwünschten Hemmung der Säuresekretion erforderlich ist. Bei der Kombination von 5-Difluormethoxy-2-[-(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol-Natrium mit Amoxycillin wird das Benzimidazol vorzugsweise (bezogen auf die frei Base) in einer Tagesdosis von 40 bis 120 mg pro Patient, insbesondere in einer Tagesdosis von 80 mg pro Patient, vorteilhafterweise in zwei Einzeldosen zu 40 mg verabfolgt. Amoxycillin wird vorzugsweise in einer Tagesdosis von 1500 bis 3000 mg pro Patient, vorteilhafterweise in zwei bis drei Einzeldosen zu 500 bis 1000 mg verabfolgt.

Patentansprüche

1. Verwendung von Verbindungen der Formel I

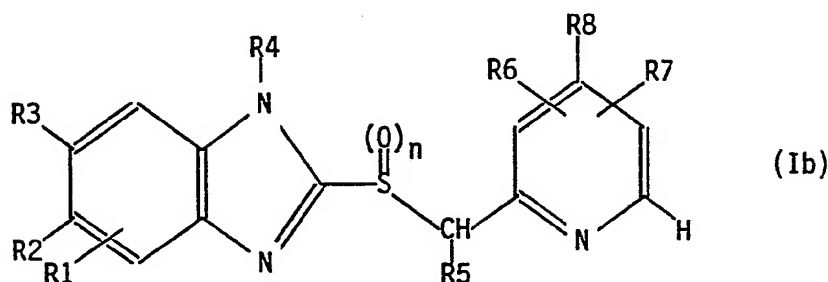


worin

- R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
 R2 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R3 ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R4 Wasserstoff oder eine unter physiologischen Bedingungen leicht abspaltbare Gruppe bedeutet,
 R5 Wasserstoff oder 1-4C-Alkyl bedeutet,
 R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
 R7 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
 R8 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet und
 n die Zahl 0 oder 1 darstellt,

und ihren pharmakologisch verträglichen Salzen zur Herstellung von oral zu verabreichenden Arzneimitteln für die Bekämpfung von Helicobacter-Bakterien.

2. Verwendung gemäß Anspruch 1 von Verbindungen der Formel Ib,



worin

- R1 Wasserstoff oder Methyl bedeutet,
 - R2 Wasserstoff, Methyl, Ethyl, Methoxy, Ethoxy, 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
 - R3 1,1,2,2-Tetrafluorethoxy, Trifluormethoxy, 2,2,2-Trifluorethoxy, Difluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 Difluormethylendioxy, 1,1,2-Trifluorethylendioxy oder 1-Chlor-1,2,2-trifluorethylendioxy bedeutet,
 - R4 Wasserstoff bedeutet,
 - R5 Wasserstoff, Methyl oder Ethyl bedeutet,
 - R6 Wasserstoff oder 1-4C-Alkyl bedeutet,
 - R7 1-4C-Alkoxy bedeutet,
 - R8 1-4C-Alkoxy bedeutet und
 - n die Zahl 0 oder 1 darstellt,
- und ihren pharmakologisch verträglichen Salzen.

3. Verwendung gemäß Anspruch 1 oder 2, dadurch gekennzeichnet, daß n die Zahl 0 bedeutet.

4. Verwendung gemäß Anspruch 1 oder 2, dadurch gekennzeichnet, daß n die Zahl 1 bedeutet.

5. Verwendung von 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol und seinen pharmakologisch verträglichen Salzen zur Herstellung von oral zu verabreichenden Arzneimitteln für die Bekämpfung von Helicobacter-Bakterien.

6. Verwendung gemäß Anspruch 1 oder 2 oder 5, dadurch gekennzeichnet, daß das oral zu verabreichende Arzneimittel in nicht magensaftresistenter Form vorliegt.

7. Oral zu verabreichendes Arzneimittel für die Bekämpfung von Helicobacter-Bakterien enthaltend 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol und/oder sein pharmakologisch verträgliches Salz in Kombination mit einem antimikrobiellen Mittel ausgewählt aus der Gruppe bestehend aus Penicillin G, Gentamycin, Erythromycin, Nitrofurazon, Nitrofurantoin, Furozolidon, Metronidazol und Amoxycillin.

8. Oral zu verabreichendes Arzneimittel für die Bekämpfung von Helicobacter pylori enthaltend 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol-Natrium in Kombination mit Amoxycillin.

9. Verwendung von 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol-Natrium zur Herstellung von oral zu verabreichenden nicht magensaftresistent formulierten Arzneimitteln für die Bekämpfung von Helicobacter-Bakterien der Spezies Helicobacter pylori.

10. Verfahren zur Herstellung von pharmazeutischen Präparaten, welche als Wirkstoff eine oder mehrere Verbindungen nach Anspruch 1 oder 2 oder 5 und übliche Träger enthalten, dadurch gekennzeichnet, daß man den auf bekannte Weise hergestellten Wirkstoff mit üblichen Trägern vermischt und in ein oral zu verabreichendes Arzneimittel für die Bekämpfung von Helicobacter-Bakterien überführt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP91/01689

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC <div style="display: flex; justify-content: space-between; margin-top: 5px;"> Int.CL.5 A61K 31/44 </div>																				
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 5px;">Minimum Documentation Searched ⁷</div> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width: 25%;">Classification System</th> <th style="width: 75%;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; padding: 5px;">Int.Cl.5</td> <td style="text-align: center; padding: 5px;">A61K</td> </tr> </table> <div style="text-align: center; margin-top: 10px; font-size: small;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div>			Classification System	Classification Symbols	Int.Cl.5	A61K														
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category ⁹</th> <th style="width: 70%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>WO, A, 8911479 (BYK GULDEN LOMBERG) 30 November 1989; see abstract; claims 1,7 (cited in the application) ---</td> <td style="text-align: center; vertical-align: top;">1-10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>WO, A, 9009175 (AKTIEBOLAGE HÄSSLE) 23 August 1990 see abstract; page 2; lines 5-14 (cited in the application) ---</td> <td style="text-align: center; vertical-align: top;">1-10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0382489 (TAKEDA CHEMICAL INDUSTRIES LTD) 16 August 1990, see abstract; claim 14 (cited in the application) ---</td> <td style="text-align: center; vertical-align: top;">1-10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Antimicrobial Agents and Chemotherapy, Vol. 28 No.6, December 1985, C.A.A. McNulty et al: "Susceptibility of clinical isolates of <i>Helicobacter pylori</i> to 11 antimicrobial agents", pages 837-838, see abstract; page 838, table 1 ---</td> <td style="text-align: center; vertical-align: top;">7,8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0282131 (THE PROCTER AND GAMBLE CO.) 14 September 1988, see abstract; page 7, lines 24-29 ---</td> <td style="text-align: center; vertical-align: top;">7,8</td> </tr> </tbody> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	WO, A, 8911479 (BYK GULDEN LOMBERG) 30 November 1989; see abstract; claims 1,7 (cited in the application) ---	1-10	A	WO, A, 9009175 (AKTIEBOLAGE HÄSSLE) 23 August 1990 see abstract; page 2; lines 5-14 (cited in the application) ---	1-10	A	EP, A, 0382489 (TAKEDA CHEMICAL INDUSTRIES LTD) 16 August 1990, see abstract; claim 14 (cited in the application) ---	1-10	A	Antimicrobial Agents and Chemotherapy, Vol. 28 No.6, December 1985, C.A.A. McNulty et al: "Susceptibility of clinical isolates of <i>Helicobacter pylori</i> to 11 antimicrobial agents", pages 837-838, see abstract; page 838, table 1 ---	7,8	A	EP, A, 0282131 (THE PROCTER AND GAMBLE CO.) 14 September 1988, see abstract; page 7, lines 24-29 ---	7,8
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																				
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 5px;">23 October 1991 (23.10.91)</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 5px;">21 November 1991 (21.11.91)</div> </td> </tr> <tr> <td style="width: 50%; padding: 5px;"> International Searching Authority <div style="text-align: center; margin-top: 5px;">European Patent Office</div> </td> <td style="width: 50%; padding: 5px;"> Signature of Authorized Officer </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 5px;">23 October 1991 (23.10.91)</div>	Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 5px;">21 November 1991 (21.11.91)</div>	International Searching Authority <div style="text-align: center; margin-top: 5px;">European Patent Office</div>	Signature of Authorized Officer														
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
P,X	European Journal of Clinical Microbiology & Infectious Diseases, Vol 10, No. 2, February 1991, S. Suerbaum et al : "Antibacterial activity of pantoprazole and omeprazole against helicobacter pylori" pages 92-93, see the whole document -----	1-6,9 10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim numbers 1-10 (partially) because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The subject matter of claims 1-10 is not supported by pharmacological data, in the absence of pharmacological data, evaluation of the technical subject matter of the claims and of prior art is questionable and subjective, it may therefore be that the closest prior art is not cited in the search report.

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9101689
SA 50728

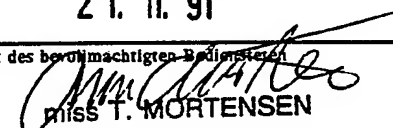
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8911479	30-11-89	AU-A- 3690289	12-12-89
		EP-A- 0415990	13-03-91
WO-A- 9009175	23-08-90	JP-A- 2209809	21-08-90
		AU-A- 5038190	05-09-90
		EP-A- 0414847	06-03-91
EP-A- 0382489	16-08-90	CA-A- 2009741	10-08-90
		JP-A- 3173817	29-07-91
		US-A- 5013743	07-05-91
EP-A- 0282131	14-09-88	AU-A- 1279388	08-09-88
		JP-A- 63290831	28-11-88
		ZA-A- 8801678	07-09-88

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 91/01689

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben) ⁶		
Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC Int.C1.5 A 61 K 31/44		
II. RECHERCHIERTE SACHGEBIETE		
Recherchierte Mindestprüfstoff ⁷		
Klassifikationssystem	Klassifikationssymbole	
Int.C1.5	A 61 K	
Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen ⁸		
III. EINSCHLAGIGE VERÖFFENTLICHUNGEN ⁹		
Art. ⁹	Kennzeichnung der Veröffentlichung ¹¹ , soweit erforderlich unter Angabe der maßgeblichen Teile ¹²	Betr. Anspruch Nr. ¹³
A	WO,A,8911479 (BYK GULDEN LOMBERG) 30. November 1989, siehe Zusammenfassung; Ansprüche 1,7 (in der Anmeldung erwähnt) ---	1-10
A	WO,A,9009175 (AKTIEBOLAGE HÄSSLE) 23. August 1990, siehe Zusammenfassung; Seite 2, Zeilen 5-14 (in der Anmeldung erwähnt) ---	1-10
A	EP,A,0382489 (TAKEDA CHEMICAL INDUSTRIES LTD) 16. August 1990, siehe Zusammenfassung; Ansprüche 14 (in der Anmeldung erwähnt) --- -/-	1-10
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>¹⁰ Besondere Kategorien von angegebenen Veröffentlichungen ¹⁰ :</p> <p>"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist</p> <p>"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist</p> <p>"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)</p> <p>"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht</p> <p>"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist</p> </div> <div style="width: 48%;"> <p>"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist</p> <p>"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden</p> <p>"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist</p> <p>"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist</p> </div> </div>		
IV. BESCHEINIGUNG		
Datum des Abschlusses der internationalen Recherche		Absendedatum des internationalen Recherchenberichts
23-10-1991		21. 11. 91
Internationale Recherchenbehörde EUROPÄISCHES PATENTAMT		Unterschrift des bevollmächtigten Beauftragten  Miss T. MORTENSEN

III. EINSCHLAGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art °	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
A	Antimicrobial Agents and Chemotherapy, Band 28. Nr. 6, Dezember 1985, C.A.A.McNulty et al.: "Susceptibility of clinical isolates of campylobacter pyloridis to 11 antimicrobial agents", Seiten 837-838, siehe Zusammenfassung; Seite 838, Tabelle 1 ---	7,8
A	EP,A,0282131 (THE PROCTER AND GAMBLE CO.) 14. September 1988, siehe Zusammenfassung; Seite 7, Zeilen 24-29 ---	7,8
P,X	European Journal of Clinical Microbiology & Infectious Diseases, Band 10, Nr. 2, February 1991, S. Suerbaum et al.: "Antibacterial activity of pantoprazole and omeprazole against helicobacter pylori", seiten 92-93, siehe das ganze Dokument -----	1-6,9, 10

WEITERE ANGABEN ZU BLATT 2

V. ☒ **BEMERKUNGEN ZU DEN ANSPRÜCHEN, DIE SICH ALS NICHT RECHERCHIERBAR ERWIESEN HABEN** ¹

Gemäß Artikel 17 Absatz 2 Buchstabe a sind bestimmte Ansprüche aus folgende Gründen nicht Gegenstand der internationalen Recherche gewesen:

1. ☐ Ansprüche Nr. _____ weil sie sich auf Gegenstände beziehen, die zu recherchieren die Behörde nicht verpflichtet ist, nämlich:

2. ☒ Ansprüche Nr. 1-10 (unvollständig) weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich:

Die Gegenstände von Ansprüche 1-10 sind nicht durch pharmakologische Daten gestützt. Durch die Abwesenheit pharmakologischer Daten wird die Beurteilung des technischen Gegenstandes der Ansprüche und des Standes der Technik fragwürdig und subjektiv. Es kann deshalb durchaus sein, dass der nächstliegende Stand der Technik nicht im Recherchenbericht zitiert wurde.

3. ☐ Ansprüche Nr. _____ weil sie abhängige Ansprüche und nicht entsprechend Satz 2 und 3 der Regel 6.4(a) PCT abgefaßt sind.

VI. ☐ **BEMERKUNGEN BEI MANGELNDER EINHEITLICHKEIT DER ERFINDUNG** ²

Die Internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich der Internationale Recherchenbericht auf alle recherchierbaren Ansprüche der Internationalen Anmeldung.
2. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchegebühren rechtzeitig entrichtet hat, erstreckt sich der Internationale Recherchenbericht nur auf die Ansprüche der Internationalen Anmeldung, für die Gebühren gezahlt worden sind, nämlich
3. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchegebühren nicht rechtzeitig entrichtet. Der Internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; sie ist in folgenden Ansprüchen erfaßt:
4. ☐ Da für alle recherchierbaren Ansprüche eine Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchegebühr gerechtfertigt hätte, hat die Internationale Recherchenbehörde eine solche Gebühr nicht verlangt.

Bemerkung hinsichtlich eines Widerspruchs

- ☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.
- ☐ Die Zahlung zusätzlicher Gebühren erfolgte ohne Widerspruch.

**ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT
ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.**

EP 9101689
SA 50728

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.

Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 11/11/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
WO-A- 8911479	30-11-89	AU-A- 3690289 EP-A- 0415990	12-12-89 13-03-91
WO-A- 9009175	23-08-90	JP-A- 2209809 AU-A- 5038190 EP-A- 0414847	21-08-90 05-09-90 06-03-91
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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(21) Internationales Aktenzeichen: PCT/EP91/02096 (22) Internationales Anmeldedatum: 6. November 1991 (06.11.91) (30) Prioritätsdaten: P 40 35 455.5 8. November 1990 (08.11.90) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Str. 2, Postf. 10 03 10, D-7750 Konstanz (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US) : KOHL, Bernhard [DE/DE]; Heinrich-v.-Tettingenstr. 35a, D-7750 Konstanz 19 (DE). (72) Erfinder (für alle Bestimmungsstaaten ausser CA US): SENN-BILFINGER, Jörg ; Säntisstraße 7, D-7750 Konstanz (DE).	(74) Gemeinsamer Vertreter: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Str. 2, Postf. 10 03 10, D-7750 Konstanz (DE). (81) Bestimmungsstaaten: AT (europäisches Patent), AU, BE (europäisches Patent), CA, CH (europäisches Patent), CS, DE, DE (europäisches Patent), DK (europäisches Patent), ES (europäisches Patent), FI, FR (europäisches Patent), GB (europäisches Patent), GR (europäisches Patent), HU, IT (europäisches Patent), JP, KR, LU (europäisches Patent), NL (europäisches Patent), NO, PL, SE (europäisches Patent), SU ⁺ , US. Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	
(54) Title: SEPARATION OF ENANTIOMERS (54) Bezeichnung: ENANTIOMERENTRENNUNG (57) Abstract The invention concerns configurationally homogeneous, enantiomerically pure pyridylmethylsulphinyl-1H-benzimidazoles, a method of preparing them, and new intermediates necessary for the preparation. (57) Zusammenfassung Die Erfindung betrifft konfigurativ einheitliche, enantiomer reine Pyridylmethylsulfinyl-1H-benzimidazole, ein Verfahren zu ihrer Herstellung und neue Zwischenprodukte, die in dem Verfahren benötigt werden.		

+ BESTIMMUNGEN DER "SU"

Die Bestimmung der "SU" hat Wirkung in der Russischen Föderation. Es ist noch nicht bekannt, ob solche Bestimmungen in anderen Staaten der ehemaligen Sowjetunion Wirkung haben.

LEDIGLICH ZUR INFORMATION

Code, die zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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Enantiomerentrennung

Anwendungsgebiet der Erfindung

Die Erfindung betrifft ein Verfahren zur Auftrennung von chiralen Pyridylmethylsulfinyl-1H-benzimidazolen in ihre Enantiomeren. Die Enantiomeren werden in der pharmazeutischen Industrie zur Herstellung von Medikamenten verwendet.

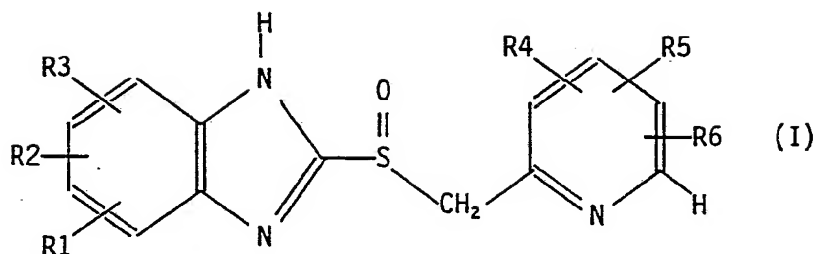
Stand der Technik

In einer Vielzahl von Patentanmeldungen und Patenten werden Pyridylmethylsulfinyl-1H-benzimidazole beschrieben, die magensäuresekretionshemmende Eigenschaften besitzen. Im Zusammenhang mit der vorliegenden Erfindung seien hier beispielsweise die folgenden Patentanmeldungen und Patente erwähnt: EP-B-5 129, EP-A-134 400 (= USP 4,555,518), EP-A-127 763 (= USP 4,560,693), EP-B-166 287 (= USP 4,758,579), EP-A-174 726, EP-A-201 575 (= USP 4,686,230), W089/05299 und W089/11479. - Es ist weiterhin bekannt, daß diese Pyridylmethylsulfinyl-1H-benzimidazole ein Chiralitätszentrum besitzen und daß sie daher in ihre Enantiomeren trennbar sein sollten. Trotz der Vielzahl von Patentanmeldungen auf dem Gebiet der Pyridylmethylsulfinyl-1H-benzimidazole ist bisher jedoch noch kein Verfahren beschrieben worden, mit dessen Hilfe die Pyridylmethylsulfinyl-1H-benzimidazole in die optischen Antipoden getrennt werden könnten. Auch die Enantiomeren der Pyridylmethylsulfinyl-1H-benzimidazole sind bisher (mangels eines geeigneten Trennverfahrens) noch nicht isoliert und charakterisiert worden.

Beschreibung der Erfindung

Es wurde nun ein Verfahren gefunden, mit dessen Hilfe die nachstehend näher bezeichneten Pyridylmethylsulfinyl-1H-benzimidazole in ihre optischen Antipoden gespalten werden können.

Das Verfahren ist dadurch gekennzeichnet, daß man Verbindungen der Formel I,



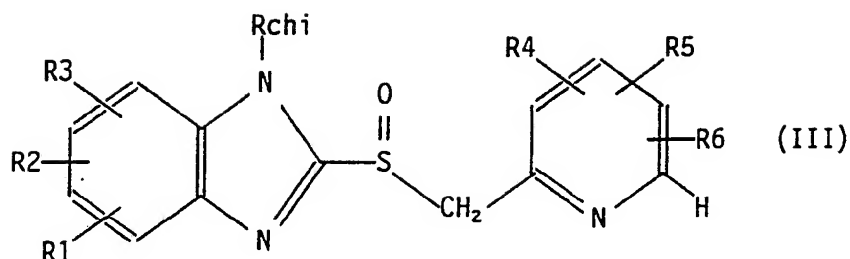
worin

- R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
 R2 Wasserstoff, Trifluormethyl, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R3 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
 R5 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet und
 R6 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet,

oder ihre Salze mit Basen mit konfigurativ einheitlichen chiralen Verbindungen der Formel II,



worin Rchi einen konfigurativ einheitlichen, chiralen Rest und X eine Abgangsgruppe darstellt, umgesetzt, das erhaltene Isomeren- bzw. Diastereomergemisch III,



worin R1, R2, R3, R4, R5 und R6 die oben angegebenen Bedeutungen haben und Rchi einen konfigurativen einheitlichen, chiralen Rest darstellt, trennt und aus den optisch reinen Diastereomeren die konfigurativen einheitlichen, optisch reinen Verbindungen I durch Solvolyse in stark saurem Medium freisetzt.

1-4C-Alkyl steht für geradkettige oder verzweigte Alkylreste; beispielsweise seien der Butyl-, i-Butyl-, sec.-Butyl-, t-Butyl-, Propyl-, Isopropyl-, Ethyl- und insbesondere der Methylrest genannt.

1-4C-Alkoxy steht für geradkettige oder verzweigte Alkoxyreste; beispielsweise seien genannt der Butoxy-, i-Butoxy-, sec.-Butoxy-, t-Butoxy-, Propoxy-, Isopropoxy-, Ethoxy- und insbesondere der Methoxyrest.

Als ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy seien beispielsweise der 1,2,2-Trifluorethoxy-, der 2,2,3,3,3-Pentafluorpropoxy-, der Perfluorethoxy- und insbesondere der 1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, der 2,2,2-Trifluorethoxy- und der Difluormethoxyrest genannt.

Wenn R2 und R3 gemeinsam ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeuten, so sind die Substituenten R2 und R3 in Nachbarpositionen am Benzoteil des Benzimidazolringes gebunden.

Als ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy seien beispielsweise der 1,1-Difluorethylendioxy- (-O-CF₂-CH₂-O-), der 1,1,2,2-Tetrafluorethylendioxy- (-O-CF₂-CF₂-O-) und insbesondere der Difluormethylendioxy- (-O-CF₂-O-) und der 1,1,2-Trifluorethylendioxyrest (-O-CF₂-CHF-O-) genannt.

Als Verbindungen der Formel II kommen prinzipiell alle chiralen, konfigurativen einheitlichen Verbindungen infrage, die mit der Verbindung I oder ihrem Anion unter Abspaltung der Abgangsgruppe X zu reagieren in der Lage sind und deren Rest R_{chi} nach der Diastereomerentrennung glatt und ohne unerwünschte Nebenreaktionen wieder abgespalten werden kann.

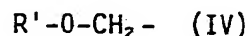
Als Abgangsgruppen X kommen insbesondere alle nucleophil ablösbaren Atome oder Gruppen, wie beispielsweise Halogenatome (J, Br oder insbesondere Cl) oder durch Veresterung (z.B. mit Sulfonsäuren) aktivierte Hydroxylgruppen ($-O-SO_2-CH_3$, $-O-SO_2-CF_3$ oder $-O-SO_2-C_6H_4-p-CH_3$) in Frage.

Als Reste R_{chi} kommen alle konfigurativen einheitlichen Reste infrage, die sich von natürlich vorkommenden oder synthetisch zugänglichen chiralen Verbindungen ableiten lassen und die solvolytisch unter sauren Bedingungen aus den Verbindungen III abgespalten werden können. Als Reste R_{chi} seien insbesondere genannt

- Glycosylreste, die sich von Glycopyranosen, Glycofuranosen oder Oligosacchariden ableiten und die gewünschtenfalls mit in der Kohlenhydratchemie üblichen Schutzgruppen teilweise oder vollständig geschützt sind, oder
- chirale, über das Sauerstoffatom verknüpfte Terpenalkoholreste, oder
- andere chirale, über das Sauerstoffatom verknüpfte Alkoholreste,

die jeweils an dem als Verknüpfungsglied fungierenden Sauerstoffatom eine Carbonylgruppe oder insbesondere eine Methylengruppe tragen.

Bevorzugte Reste R_{chi} sind Reste der Formel IV



worin R' gemeinsam mit dem Sauerstoffatom, woran es gebunden ist, einen Glycosylrest, einen chiralen Terpenalkoholrest, oder einen sonstigen chiralen Alkoholrest darstellt.

Als Glycosylreste R'-O- seien beispielsweise die Reste genannt, die sich von natürlich vorkommenden Mono- oder Disacchariden, wie Arabinose, Fructose, Galactose, Glucose, Lactose, Mannose, Ribose, Xylose, Maltose, Sorbose oder N-Acetyl-D-glucosamin herleiten.

Als chirale Terpenalkoholreste R'-O- seien insbesondere solche Reste genannt, die sich von einem natürlich vorkommenden oder synthetisch leicht zugänglichen Terpenalkohol herleiten. Als beispielhafte Terpenalkohole seien hierbei genannt: Isopulegol, Neomenthol, Isomenthol, Menthol, Carveol, Dihydrocarveol, Terpinen-4-ol, Mirtenol, Citronellol, Isoborneol, Borneol, Isopinocampheol und insbesondere Fenchol.

Als sonstige chirale Alkoholreste R'-O- seien beispielsweise die Reste genannt, die sich von folgenden Alkoholen herleiten: Mandelsäureester, Cinchonidin, Cinchonin, Ephedrin, Serinmethylester, Sitosterol, 3-Hydroxy-2-methyl-propionsäuremethylester und Milchsäureethylester.

Ein besonderes bevorzugter Rest R_{chi} ist der Fenchyloxymethylrest.

Die Umsetzung der Verbindung I mit der Verbindung II erfolgt auf eine dem Fachmann vertraute Weise. Zur Erhöhung der Nucleophilie der Verbindungen I ist es zweckmäßig, diese zu deprotonieren, d.h. von den Salzen der Verbindungen I mit Basen auszugehen. Als Beispiele für basische Salze seien Natrium-, Kalium-, Calcium-, Aluminium-, Magnesium-, Titan-, Ammonium- oder Guanidiniumsalze erwähnt, die beispielsweise durch Umsetzung der Verbindungen I mit den entsprechenden Hydroxiden (z.B. Natriumhydroxid oder Kaliumhydroxid) auf übliche Weise erhalten werden können.

Die Umsetzung der Verbindungen I mit Verbindungen II wird in inerten, protischen oder aprotischen Lösungsmitteln durchgeführt. Als solche eignen sich beispielsweise Methanol, Isopropanol, Dimethylsulfoxid, Aceton, Acetonitril, Dioxan, Dimethylformamid und vorzugsweise N-Methylpyrrolidon.

Die Umsetzung wird - in Abhängigkeit von der Reaktivität der Verbindung II - vorzugsweise bei Temperaturen zwischen -30 °C und +100 °C, insbesondere bei Temperaturen zwischen 0 °C und 50 °C durchgeführt.

Die Trennung des nach der Umsetzung von I mit II erhaltenen Diastereomerengemisches erfolgt in an sich bekannter Weise, beispielsweise durch Chromatografie an geeigneten Säulen oder vorzugsweise durch fraktionierte Kristallisation.

Aufgrund der Prototropie im Benzimidazolteil der Verbindungen I (die 5- und 6-Positionen einerseits bzw. die 4- und 7-Positionen andererseits sind zueinander

identisch) entstehen bei der Umsetzung mit den Verbindungen II bei entsprechendem Substitutionsmuster im Benzimidazol Isomerengemische. Zweckmäßigerweise werden die Isomeren noch vor Trennung der Diastereomeren voneinander getrennt, beispielsweise durch Säulenchromatographie an geeignetem Trägermaterial (z.B. Kieselgel) und mit geeigneten Elutionsmitteln (z.B. Ethylacetat).

Die Freisetzung der konformativ einheitlichen Verbindungen I aus den optisch reinen Diastereomeren III erfolgt durch Solvolyse unter stark sauren Bedingungen. Als für die Solvolyse geeignete Reagenzien seien beispielsweise starke, höherkonzentrierte Säuren (z.B. 60-100 %-ige Schwefelsäure, konzentrierte Salzsäure, wasserfreie oder wasserhaltige Tetrafluorborsäure, Methansulfonsäure, Trifluormethansulfonsäure, Phosphorsäure oder Perchlorsäure), bevorzugt ca. 90 %-ige Schwefelsäure genannt. Die Freisetzung erfolgt vorzugsweise bei Temperaturen zwischen 0° und 40° C. Bei der auf die Freisetzung folgenden Aufarbeitung wird vorteilhafterweise so verfahren, daß der pH-Wert möglichst rasch erhöht wird, beispielsweise durch Einbringen der stark sauren Lösung in Pufferlösung oder bevorzugt in Lauge.

Die Verbindungen der Formel II sind bekannt bzw. sie sind auf eine für den Fachmann vertraute Weise aus bekannten Verbindungen auf analoge Weise zugänglich. So können beispielsweise die Verbindungen II, in denen R_{chi} die Bedeutung der Formel IV hat und X ein Chloratom darstellt, durch Chlormethylierung entsprechender Alkohole [z.B. in Analogie zu R.C. Ronald et al., J. Org. Chem. 45 (1980) 2224] hergestellt werden.

Die Verbindungen der Formel III sind neu und ebenfalls Gegenstand der Erfindung.

Die konfigurativ einheitlichen, optisch reinen Verbindungen der Formel I sind ebenfalls neu und daher auch Gegenstand der Erfindung.

Als beispielhafte, durch das erfindungsgemäße Verfahren herstellbare, optisch reine Verbindungen der Formel I und als dazugehörige erfindungsgemäße Zwischenprodukte III seien anhand der Substituentenbedeutungen in den obenstehenden Formeln I bzw. III die folgenden Verbindungen der nachstehenden Tabelle 1 besonders erwähnt:

Tabelle 1

R1	R2, R3		R4	R5	R6
H	5-CF ₃	H	H	H	4-OCH ₃
H	5-CF ₃	H	3-CH ₃	H	4-OCH ₃
H	5-CF ₃	H	3-CH ₃	5-CH ₃	4-OCH ₃
H	5-OCH ₃	H	3-CH ₃	5-CH ₃	4-OCH ₃
H	5,6-O-CH ₂ -O-		H	H	4-OCH ₃
H	5,6-O-CH ₂ -CH ₂ -O-		H	H	4-OCH ₃
H	H	5-OCF ₃	H	H	4-OCH ₃
H	H	5-OCF ₃	3-CH ₃	H	4-OCH ₃
H	H	5-OCF ₃	H	5-CH ₃	4-OCH ₃
H	H	5-OCF ₂ CF ₂ H	H	H	4-OCH ₃
H	H	5-OCF ₂ CF ₂ H	3-CH ₃	H	4-OCH ₃
H	H	5-OCF ₃	3-CH ₃	5-CH ₃	4-OCH ₃
H	H	5-OCH ₂ CF ₃	3-CH ₃	H	4-OCH ₃
H	H	5-OCF ₂ H	3-CH ₃	H	4-OCH ₃
H	5-OCF ₂ H	6-OCF ₂ H	H	H	4-OCH ₃
H	5-OCF ₂ H	6-OCF ₂ H	3-CH ₃	H	4-OCH ₃
H	5-OCH ₃	6-OCF ₂ H	3-CH ₃	H	4-OCH ₃
H	H	5-OCF ₂ Cl	H	H	4-OCH ₃
H	5,6-O-CF ₂ -O-		H	H	4-OCH ₃
H	5,6-O-CF ₂ -O-		3-CH ₃	H	4-OCH ₃
H	5,6-O-CF ₂ -CHF-O-		H	H	4-OCH ₃
H	5,6-O-CF ₂ -CHF-O-		3-CH ₃	H	4-OCH ₃
H	5,6-O-CF ₂ -O-		H	5-CH ₃	4-OCH ₃
H	5,6-O-CF ₂ -CHF-O-		3-CH ₃	5-CH ₃	4-OCH ₃
H	5,6-O-CF ₂ -CFC1-O-		3-CH ₃	H	4-OCH ₃
4-CH ₃	6-CH ₃	5-OCF ₂ H	3-CH ₃	H	4-OCH ₃
H	5-OCH ₃	6-OCF ₂ H	H	H	4-OCH ₃
H	H	5-OCF ₂ CF ₂ H	H	H	4-OCH ₃
H	5,6-O-CF ₂ -O-		H	H	4-OCH ₃
H	H	5-OCF ₂ CC1FH	H	H	4-OCH ₃
H	H	5-OCF ₂ CC1FH	H	H	4-OCH ₃
H	H	5-OCF ₂ CC1FH	3-CH ₃	H	4-OCH ₃
4-CH ₃	6-CH ₃	5-OCF ₂ H	H	3-OCH ₃	4-OCH ₃

Fortsetzung Tabelle 1

R1	R2, R3	R4	R5	R6
H	H 5-OCF ₂ H	H	3-OCH ₃	4-OCH ₃
H	H 5-OCF ₂ H	3-CH ₃	5-OCH ₃	4-OCH ₃
H	H 5-OCF ₃	3-CH ₃	5-OCH ₃	4-OCH ₃
H	H 5-OCF ₂ CF ₂ H	H	3-OCH ₃	4-OCH ₃
H	H 5-OCH ₂ CF ₃	H	3-OCH ₃	4-OCH ₃
H	5-OCH ₃ 6-OCF ₂ H	H	3-OCH ₃	4-OCH ₃
H	5,6-0-CF ₂ -0-	H	3-OCH ₃	4-OCH ₃
H	5,6-0-CF ₂ -CHF-0-	H	3-OCH ₃	4-OCH ₃
H	H 5-OCF ₃	H	5-OCH ₃	4-OCH ₃
H	H 5-OCF ₂ CF ₂ H	H	5-OCH ₃	4-OCH ₃
H	5,6-0-CF ₂ -0-	H	5-OCH ₃	4-OCH ₃
H	5,6-0-CF ₂ -0-	H	4-OCH ₃	5-OCH ₂ -<O>
H	H 5-OCF ₂ H	H	3-OCH ₃	4-OCH ₂ -<O>
H	H 5-OCF ₂ H	H	4-OCH ₃	3-OCH ₂ -<O>
H	H 5-OCF ₂ H	3-CH ₃	4-OCH ₃	5-OCH ₂ -<O>
H	H 5-OCF ₂ H	H	3-OCH ₃	4-OCH ₂ CF ₃
H	H 5-OCF ₂ H	H	3-CH ₃	4-OCH ₂ CF ₃
H	H 5-OCH ₂ CF ₃	H	3-CH ₃	4-OCH ₂ CF ₃
H	5,6-0-CF ₂ -0-	H	3-CH ₃	4-OCH ₂ CF ₃

Besonders bevorzugte, durch das erfindungsgemäße Verfahren herstellbare Verbindungen sind die Verbindungen

(+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(-)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-2-{[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol und
(-)-2-{[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol,
und ihre Salze mit Basen.

Die folgenden Beispiele dienen der näheren Erläuterung der Erfindung. Die Abkürzung h steht für Stunde(n), Schmp. für Schmelzpunkt.

Beispiele1. (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol

Zu einer Lösung von 50 g (0,123 Mol) (±)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-Na-Salz in 125 ml N-Methylpyrrolidon tropft man bei einer Temperatur von 25-35 °C innerhalb einer Stunde 27,5 g (0,136 Mol) (+)-Fenchyl-chlormethylether zu. Nach 6 h wird mit 500 ml Wasser verdünnt, der pH-Wert auf 9,0 gestellt und dreimal mit je 100 ml Dichlormethan extrahiert. Die vereinigten organischen Phasen werden mit Wasser gewaschen, getrocknet und im Vakuum vollständig eingeengt. Der ölige Rückstand wird an Kieselgel chromatographiert (Laufmittel: Ethylacetat). Man isoliert 25,2 g (74 %) eines Diastereomerengemisches aus (+)- und (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol als blaßgelbes, allmählich kristallisierendes Öl (Rf.-Wert in Ethylacetat ca. 0,85). Viermalige Umkristallisation aus Ethylacetat/Diisopropylether liefert die Titelverbindung (9,0 g, 71,4 %) in Form farbloser Kristalle vom Schmp. 138-139 °C $\{[\alpha]_D^{22} = +155,2^{\circ} (c=1, \text{Chloroform})\}$.

2. (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol

1,0 g (1,8 mMol) (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol werden portionsweise bei 5-10 °C unter Rühren in 7 ml 90 %-ige Schwefelsäure eingetragen. Nach vollständiger Auflösung wird das Reaktionsgemisch unter Kühlung in 8N Natronlauge eingetropft, der pH auf 7,5 gestellt und mehrmals mit Dichlormethan extrahiert. Die vereinigten Extrakte werden mit Wasser gewaschen, über Magnesiumsulfat getrocknet und im Vakuum vollständig eingeengt. Der rote, ölige Rückstand wird über Kieselgel chromatographiert (Dichlormethan/Methanol) und anschließend aus Diisopropylether kristallisiert. Man erhält 0,3 g (44 %) der Titelverbindung als farbloses Kristallisat vom Schmp. 147-148 °C (Zers.) $\{[\alpha]_D^{22} = +146,0^{\circ} (c=0,5, \text{Acetonitril/Methanol 1:1})\}$.

3. (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-
[(-)-fenchyloxymethyl]-benzimidazol

Nach der in Beispiel 1 beschriebenen Arbeitsweise erhält man durch Umsetzung von 28 g (0,069 Mol) (\pm)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl}-1H-benzimidazol-Na-Salz mit 16,5 g (0,084 Mol) (-)-Fenchylchloromethylether in 75 ml N-Methylpyrrolidon nach Chromatographie an Kieselgel (Dichlormethan/Methanol) 11,0 g (58 %) eines Diastereomerenengemisches aus (+)- und (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(-)-fenchyloxymethyl]-benzimidazol. Mehrmalige Umkristallisation aus Ethylacetat/Diisopropylether liefert die Titelverbindung in Form farbloser Kristalle (4,0 g, 72 %) vom Schmp. 138-139 °C $\{[\alpha]_D^{22} = -152,8^{\circ} \text{ (c=1, Chloroform)}\}$.

4. (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-
benzimidazol

Nach der in Beispiel 2 beschriebenen Arbeitsweise erhält man aus 1 g (1,8 mMol) (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(-)-fenchyloxymethyl]-benzimidazol in 7 ml 90 %-iger Schwefelsäure 0,25 g (36 %) der Titelverbindung vom Schmp. 144-145 °C (Zers.) $\{[\alpha]_D^{22} = -144,4^{\circ} \text{ (c= 0,5, Acetonitril/Methanol 1:1)}\}$.

5. (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1-
[(+)-fenchyloxymethyl]-benzimidazol

Nach der in Beispiel 1 beschriebenen Arbeitsweise erhält man aus (\pm)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-Na-Salz (60 mMol) in 80 ml N-Methylpyrrolidon nach Chromatographie an Kieselgel (Ethylacetat) nach mehrmaliger Umkristallisation aus Ethylacetat/Diisopropylether 3,1 g (40 %) der Titelverbindung in Form farbloser Kristalle vom Schmp. 161 °C (Zers.) $\{[\alpha]_D^{22} = +103,0^{\circ} \text{ (c=1, Chloroform)}\}$.

6. (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol

Nach der in Beispiel 2 beschriebenen Arbeitsweise erhält man aus 0,51 g (1 mmol) (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-[(+)-fenchyloxymethyl]-benzimidazol in 4 ml 90 %-iger Schwefelsäure 0,15 g (43 %) der Titelverbindung als amorphen Feststoff $\{[\alpha]_D^{22} = +165^0\}$ (c= 0,5, Chloroform).

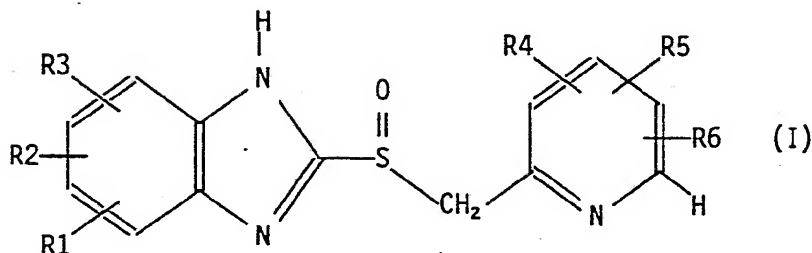
Gewerbliche Anwendbarkeit

Nach dem erfindungsgemäßen Verfahren können Pyridylmethylsulfinyl-1H-benzimidazole erstmals in ihre optischen Antipoden aufgespalten werden. Als besonders überraschend ist hierbei die Tatsache zu werten, daß die Freisetzung der optisch reinen Verbindungen aus den Diastereomeren mit Hilfe hochkonzentrierter Mineralsäuren vorgenommen wird, obwohl bekannt ist, daß es sich bei den Pyridylmethylsulfinyl-1H-benzimidazolen um sehr säurelabile Verbindungen handelt.

Die erfindungsgemäß hergestellten Verbindungen werden als Wirkstoffe in Arzneimitteln für die Behandlung von Magen- und Darmerkrankungen eingesetzt. Bezüglich der Anwendungsweise und Dosierung der Wirkstoffe wird z.B. auf das europäische Patent 166 287 verwiesen.

Patentansprüche

1. Konfigurativ einheitliche, optisch reine Verbindungen der Formel I



worin

- R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,
 R2 Wasserstoff, Trifluormethyl, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R3 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R3 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
 R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
 R5 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet und
 R6 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet,
 und ihre Salze mit Basen.

2. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

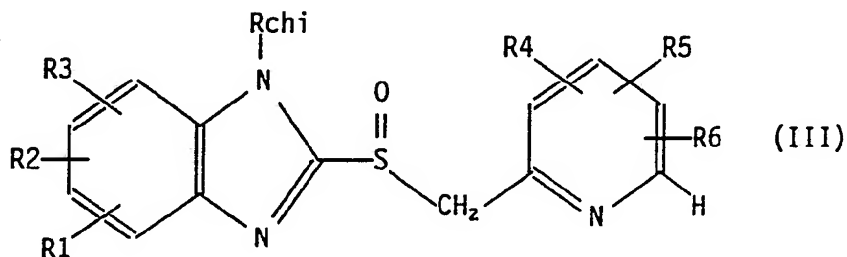
- (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
 (-)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
 (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,

(-)-5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,
 (+)-2-[[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol und
 (-)-2-[[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,
 und ihren Salzen mit Basen.

3. Verfahren zur Herstellung von konfiguratив einheitlichen, optisch reinen Verbindungen der Formel I nach Anspruch 1 und ihren Salzen, dadurch gekennzeichnet, daß man Racemate von Verbindungen der Formel I, worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben, oder ihre Salze mit Basen, mit konfiguratив einheitlichen, chiralen Verbindungen der Formel II,



worin Rchi einen konfiguratив einheitlichen, chiralen Rest und X eine Abgangsgruppe darstellt, umgesetzt, das erhaltene Isomeren- bzw. Diastereomergemisch III,



worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben und Rchi einen konfiguratив einheitlichen, chiralen Rest darstellt, trennt und aus den optisch reinen Diastereomeren die konfiguratив einheitlichen, optisch reinen Verbindungen I durch Solvolyse in stark saurem Medium freisetzt und gewünschtenfalls anschließend in die Salze mit Basen überführt.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Verbindung ausgewählt aus der Gruppe bestehend aus

(+)-5-Difluormethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,

(-)-5-Difluormethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,

(+)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,

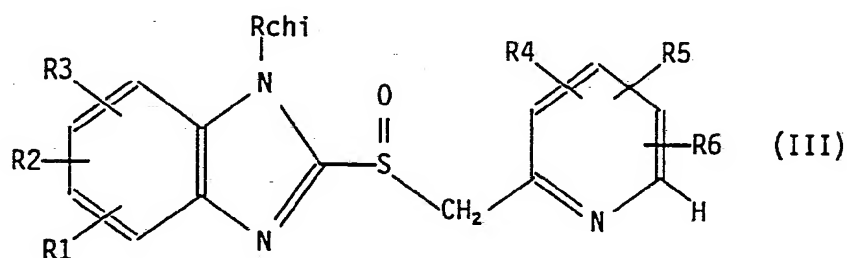
(-)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol,

(+)-2-[[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazol und

(-)-2-[[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl]sulfinyl-1H-benzimidazol,

oder ihr Salz mit Basen herstellt.

5. Zwischenprodukte der Formel III,



worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben und Rchi einen konfiguratativ einheitlichen, chiralen Rest darstellt.

6. Zwischenprodukte nach Anspruch 5, worin Rchi einen Fenchyloxymethylrest darstellt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP91/02096

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5	C07D 401/12, C07B 57/00	
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	ANALYTICAL BIOCHEMISTRY, Vol. 136, 1984 S. Allenmark et al: "Direct Optical Resolution of a Series of Pharmacologically Active Racemic Sulfoxides by High-Performance Liquid Affinity Chromatography", see page 293- page 297	1-2
A	US, A, 4686230 (RAINER ET AL) 11 August 1987, see column 2 and example 8	1-2
X	ACTA CHEMICA SCANDINAVICA, Vol. 43, 1989 A. Brändström et al: "Chemical Reactions of Omeprazole and Omeprazole Analogues. V. The Reaction of N-alkylated Derivatives of Omeprazole Analogues with 2-Mercaptoethanol", pages 587-594; see pages 592-594	5
A	US, A, 4873337 (SIH ET AL) 10 October 1989, see example 27 and claim 3	5

<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
5 February 1992 (05.02.92)	17 March 1992 (17.03.92)	
International Searching Authority	Signature of Authorized Officer	
European Patent Office		

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 91/02096**

SA 52741

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/11/91. The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4686230	11/08/87	AU-D- 5198886	15/05/86
		EP-A- 0201575	20/11/86
		JP-T- 62500664	19/03/87
		WO-A- 86/02646	09/05/86
US-A- 4873337	10/10/89	AU-B- 568441	24/12/87
		AU-D- 4669085	10/04/86
		EP-A- 0176308	02/04/86

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 91/02096

I. KLASSEFIZKATION DES ANMELDUNGSGENSTANDS (bei mehreren Klassefizierungssymbolen sind alle anzugeben) ⁶ Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassefizierung und der IPC Int.Cl.5 C 07 D 401/12, C 07 B 57/00														
II. RECHERCHIERTE SACHGEBIETE <div style="text-align: center; margin-top: 5px;">Recherchierter Mindestprüfstoff⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%; padding: 5px;">Klassifikationssystem</td> <td style="padding: 5px;">Klassifikationssymbole</td> </tr> <tr> <td style="padding: 5px;">Int.Cl.5</td> <td style="padding: 5px;">C 07D</td> </tr> </table> <div style="text-align: center; margin-top: 5px;">Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen⁸</div>			Klassifikationssystem	Klassifikationssymbole	Int.Cl.5	C 07D								
Klassifikationssystem	Klassifikationssymbole													
Int.Cl.5	C 07D													
III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; padding: 5px;">Art *</th> <th style="width: 70%; padding: 5px;">Kennzeichnung der Veröffentlichung¹¹, soweit erforderlich unter Angabe der maßgeblichen Teile¹²</th> <th style="width: 20%; padding: 5px;">Betr. Anspruch Nr.¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> ANALYTICAL BIOCHEMISTRY, Band. 136, 1984 S. Allenmark et al: "Direct Optical Resolution of a Series of Pharmacologically Active Racemic Sulfoxides by High-Performance Liquid Affinity Chromotography", siehe Seite 293 - Seite 297 <div style="text-align: center;">--</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-2</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;"> US, A, 4686230 (RAINER ET AL) 11 August 1987, Siehe Spalte 20 und Beispiel 8 <div style="text-align: center;">--</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-2</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;"> ACTA CHEMICA SCANDINAVICA, Band. 43, 1989 A. Brändström et al: "Chemical Reactions of Omeprazole and Omeprazole Analogues. V. The Reaction of N-alkylated Derivatives of Omeprazole Analogues with 2-Mercaptoethanol", Seiten 587-594. Siehe Seiten 592-594 <div style="text-align: center;">--</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">5</td> </tr> </table> <div style="margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>* Besondere Kategorien von angegebenen Veröffentlichungen¹⁰ :</p> <p>"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist</p> <p>"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist</p> <p>"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)</p> <p>"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht</p> <p>"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist</p> </div> <div style="width: 48%;"> <p>"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist</p> <p>"X" Veröffentlichung von besonderer Bedeutung, die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden</p> <p>"Y" Veröffentlichung von besonderer Bedeutung, die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist</p> <p>"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist</p> </div> </div> </div>			Art *	Kennzeichnung der Veröffentlichung ¹¹ , soweit erforderlich unter Angabe der maßgeblichen Teile ¹²	Betr. Anspruch Nr. ¹³	X	ANALYTICAL BIOCHEMISTRY, Band. 136, 1984 S. Allenmark et al: "Direct Optical Resolution of a Series of Pharmacologically Active Racemic Sulfoxides by High-Performance Liquid Affinity Chromotography", siehe Seite 293 - Seite 297 <div style="text-align: center;">--</div>	1-2	A	US, A, 4686230 (RAINER ET AL) 11 August 1987, Siehe Spalte 20 und Beispiel 8 <div style="text-align: center;">--</div>	1-2	X	ACTA CHEMICA SCANDINAVICA, Band. 43, 1989 A. Brändström et al: "Chemical Reactions of Omeprazole and Omeprazole Analogues. V. The Reaction of N-alkylated Derivatives of Omeprazole Analogues with 2-Mercaptoethanol", Seiten 587-594. Siehe Seiten 592-594 <div style="text-align: center;">--</div>	5
Art *	Kennzeichnung der Veröffentlichung ¹¹ , soweit erforderlich unter Angabe der maßgeblichen Teile ¹²	Betr. Anspruch Nr. ¹³												
X	ANALYTICAL BIOCHEMISTRY, Band. 136, 1984 S. Allenmark et al: "Direct Optical Resolution of a Series of Pharmacologically Active Racemic Sulfoxides by High-Performance Liquid Affinity Chromotography", siehe Seite 293 - Seite 297 <div style="text-align: center;">--</div>	1-2												
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IV. BESCHEINIGUNG <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Datum des Abschlusses der internationalen Recherche <div style="text-align: center; margin-top: 5px;">5. Februar 1992</div> </td> <td style="width: 50%; padding: 5px;"> Absendedatum des internationalen Recherchenberichts <div style="text-align: center; margin-top: 5px;">17. 03. 92</div> </td> </tr> <tr> <td style="padding: 5px;"> Internationale Recherchenbehörde <div style="text-align: center; margin-top: 10px;">Europäisches Patentamt</div> </td> <td style="padding: 5px;"> Unterschrift des bevollmächtigten Bediensteten <div style="text-align: center; margin-top: 10px;"> Natalie Weinberg </div> </td> </tr> </table>			Datum des Abschlusses der internationalen Recherche <div style="text-align: center; margin-top: 5px;">5. Februar 1992</div>	Absendedatum des internationalen Recherchenberichts <div style="text-align: center; margin-top: 5px;">17. 03. 92</div>	Internationale Recherchenbehörde <div style="text-align: center; margin-top: 10px;">Europäisches Patentamt</div>	Unterschrift des bevollmächtigten Bediensteten <div style="text-align: center; margin-top: 10px;"> Natalie Weinberg </div>								
Datum des Abschlusses der internationalen Recherche <div style="text-align: center; margin-top: 5px;">5. Februar 1992</div>	Absendedatum des internationalen Recherchenberichts <div style="text-align: center; margin-top: 5px;">17. 03. 92</div>													
Internationale Recherchenbehörde <div style="text-align: center; margin-top: 10px;">Europäisches Patentamt</div>	Unterschrift des bevollmächtigten Bediensteten <div style="text-align: center; margin-top: 10px;"> Natalie Weinberg </div>													

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)		
Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile ...	Betr. Anspruch Nr.
A	US, A, 4873337 (SIH ET AL) 10 Oktober 1989, Siehe Beispiel 27 und Anspruch 3 -- -----	5

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR. PCT/EP 91/02096

SA 52741

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben.

Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 30/11/91
 Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentedokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
US-A- 4686230	11/08/87	AU-D- 5198886	15/05/86
		EP-A- 0201575	20/11/86
		JP-T- 62500664	19/03/87
		WO-A- 86/02646	09/05/86
US-A- 4873337	10/10/89	AU-B- 568441	24/12/87
		AU-D- 4669085	10/04/86
		EP-A- 0176308	02/04/86

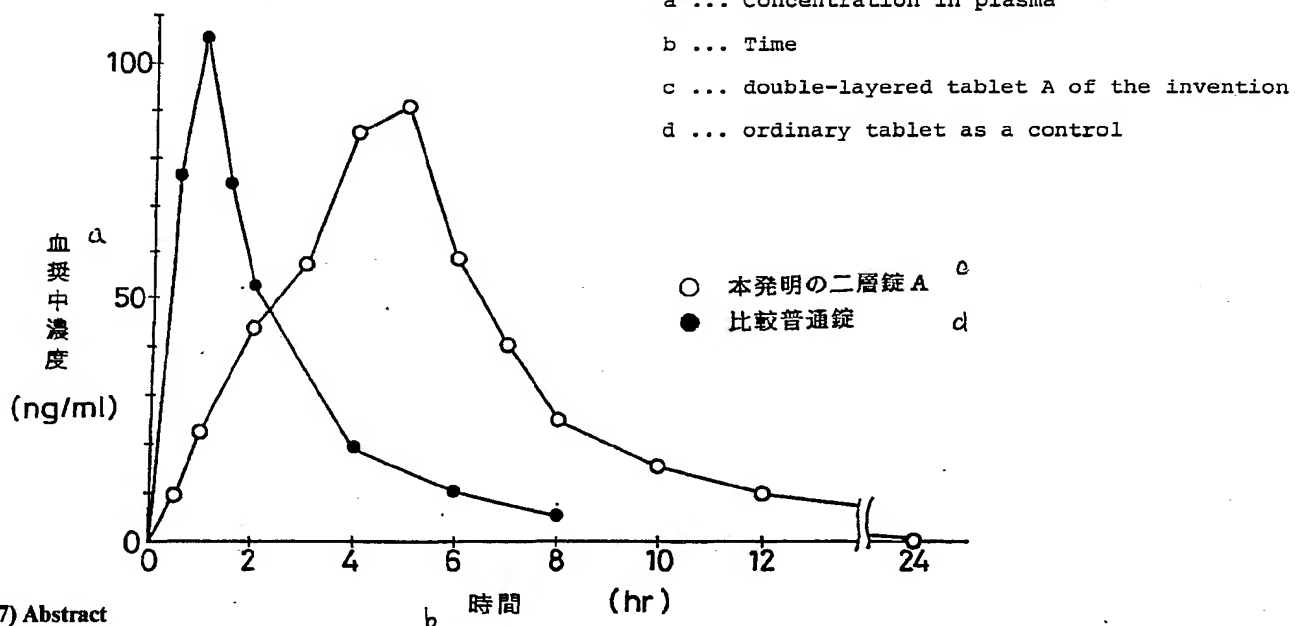


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(54) Title : LONG-ACTING PREPARATION

(54) 発明の名称 持続性製剤



(57) Abstract

A long-acting preparation having a remarkably excellent long-lasting efficacy in peroral absorption, comprising a double-layered tablet consisting of a rapidly soluble part containing a principal agent as the inner layer and a sustained-release part containing a principal agent as the outer layer.

(57) 要約

本発明の持続性製剤は、主薬含有速溶部によって内層を構成し、外層を主薬含有徐放部とした複層錠であるから、経口吸収における長時間持続性は極めて優れたものとなった。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT	オーストリア	FI	フィンランド	MR	モーリタニア
AU	オーストラリア	FR	フランス	MW	マラウイ
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BG	ブルガリア	GR	ギリシャ	PL	ポーランド
BJ	ベナン	HU	ハンガリー	PT	ポルトガル
BR	ブラジル	IE	アイルランド	RO	ルーマニア
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CS	チェコスロヴァキア	LU	ルクセンブルグ	TD	チャード
CZ	チェコ共和国	MC	モナコ	TG	トーゴ
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DK	デンマーク	ML	マリ	US	米国
ES	スペイン	MN	モンゴル		

明 細 書

1

発明の名称

持続性製剤

技術分野

5

本発明は、2層以上の多層構造からなる錠剤タイプの持続性製剤に関し、詳細には外層を徐放性としてそれ自身にタイム・ラグを持った持続性を持たせると共に、内層を速溶性としタイム・ラグを置いて溶出されてきた後においても引続き治療上もしくは予防上有効な高い生体内濃度を与え続けることができる様な持続性製剤に関するものである。

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背景技術

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薬物の経口投与においては、消化管内に入った経口製剤からの主薬の放出状況を制御することが可能である。即ち適切な制御が行なわれるならば、服用間隔を長くとっても次回服用までの長時間に亘って治療上もしくは予防上有効な高い生体内濃度を保持することが可能となって服用回数の軽減を達成することができる。また生体内濃度が一時的に急上昇したときには毒性や副作用等の危険が増大する様な薬物にあっては、適切な放出制御を行うことによって薬物の生体内濃度を上記危険の生じない範囲であってしかも治療上もしくは予防上有効な生体内濃度に保つことが強く望まれる。

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その為薬物の経口製剤については新しいDDS (Drug Delivery System) の観点から上記の様な放出制御が検討され、種々の持続性製剤が開発されている。従来提供されてきた持続性薬剤としては、例えば薬物を含む顆粒に水不溶性もしくは難溶

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1 性の皮膜を施したものや、薬物を同じく水不溶性もしくは難
溶性の連続マトリックス中に分散させた所謂マトリックス錠
等が挙げられ、これらは薬物が皮膜やマトリックス中を拡散
していくときの抵抗によって放出制御を行なうという考え方
5 の下に種々の製剤設計がなされている。より詳細に言えば、
これらの製剤における薬物放出の様式は、水の浸透に伴って
生じる製剤内における薬物濃度勾配を駆動力とするものであ
る（拡散律速）為、溶出後期になると濃度勾配の緩和や拡散
距離の増大等に起因して溶出速度の減少が認められる。

10 持続性製剤としては上記の他腸溶性製剤があり、これはpH
による溶解度の違いを利用して胃から腸管へ向かう過程で薬
物を徐放させていくものである。しかしながら体内のある特
定部に着目しても、pHは個人差、年令差、胃内食物の量、
日内変動、精神状態による変動等を受け易いものである為、
15 薬物の放出制御が非常に不確実なものにならざるを得ないとい
う欠点がある。

本出願人においては、上記の様な従来技術の欠点に鑑み、
薬物放出速度が一定（0次放出）に近く、またpH条件の変
動や薬物崩壊試験時の攪拌強度の変化等による影響を受け難
い製剤を開発すべくかねてより研究を行ってきた。その成果
20 として、日本特許公開昭和61年第24516号や同62年第10012
号等に記載されている様に、主薬を含有する崩壊性の顆粒お
よびワックス類からなる持続性製剤を開発し開示している。
この製剤は、特に主薬を含有する崩壊性の顆粒表面にワック
ス類を施した後に打錠される錠剤を含むものであり、体液中
25

1 でワックス部分が徐々に溶解し、錠剤表面部の顆粒が体液に
接触して順次薬物を放出していくものであるが、顆粒に配合
される崩壊剤の量とワックスの量を調節することによって徐
5 放の程度を制御し得るという利点を有している。この様な錠
剤を提供することによって、薬物の徐放制御が一層高精度に
行なわれるに至ったが、一方では、徐放制御によって薬物の
一部が遅れて放出されたとしても、当該放出部位が小腸下部
の様に吸収効率の低い消化管部位であったりすると、薬物の
10 吸収が不十分になって、せっかくの徐放化効果を十分に享受
し得なくなるという問題が出てくる。薬物が難溶性医薬であ
る場合にはこの問題が一層顕著なものとなってくる。

 本発明はこの様な事情に着目してなされたものであって、
主薬の放出に時間差を与えることによって薬物の徐放制御を
行うと共に、遅れて放出されてくる薬物が小腸下部の様な吸
15 収効率の低い部分に放出されたとしても、当該部位において
十分吸収されて生体内濃度を治療上もしくは予防上必要な濃
度に形成維持することができる様な錠剤の提供を目的とする
ものである。

発明の開示

20 上記目的を達成することのできた本発明の錠剤は、2層ま
たは必要に応じてそれ以上の多層構成とすることが可能な複
層構造を有し、内層については、主薬を含有する速溶部によって
構成することとし、一方外層については、上記主薬と同一又
は類似の主薬を含有する徐放部によって構成することを基本
25 要旨とするものである。

1 図面の簡単な説明

第1図はin vitroの溶出試験結果を示すグラフである。

第2, 3図はin vitroの溶出試験において実験条件を種々変更したときの結果を示すグラフである。

5 第4図はin vivoの経口吸収性を示すグラフである。

発明を実施する為の最良の形態

本発明錠剤の構成は前記の様に2層または2層以上とすることが可能な多層錠であるが、もっとも代表的なものは2層タイプである。従って以下の説明においては2層タイプの場合を中心に、即ち内層と外層からなる場合について説明するが、外層の更に外側へ着色層、糖衣層、或は保護層を設けたり、或は同じく外層の更に外側へ主薬を含み且つ優れた速溶性を有する速効層を設けたり、或は外層と内層の間に速溶部と徐放部の中間程度の溶解・放出性を有する主薬含有中間層を設けること等が排除される訳ではない。従って本明細書で用いる「内層」および「外層」の用語は、前記した速溶部と徐放部の位置関係のみに基づいて用いられるものであり、絶対的意味を有する訳ではない。尚本発明錠剤の各層に含有される主薬は全てが同一化合物である場合の他、同一薬物を持つ他の化合物である場合、並びに類似薬効を持つ他の化合物である場合を包含するが、以下同一薬効同一化合物である場合を代表的に取り上げて説明する。

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尚上記説明における同一化合物とは、該化合物が酸又は塩基であるときに、種々の塩基又は酸と塩を形成している場合を包含するものとし、塩形成の為の塩基や酸が異なっていて

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1 も同一化合物と考えるべきである。

従って本発明錠剤の基本的構成は、主薬含有速溶部を錠剤中心側に配し、主薬含有徐放部を錠剤外周側に配した点に存在し、本発明錠剤が経口的に消化管内に投与された後は、まず外周側の主薬含有徐放部が体液によって徐々に崩壊しつつ消化管内を順次下降し、相当の時間が経過した後に主薬含有速溶部の一部が体液と接触しはじめ、当該接触部から速溶部の崩壊が速やかに開始される。ここで服用後の時間経過を服用初期、中期、後期に分けて説明することとすると、服用初期から中期にかけては徐放部から徐々に崩壊放出されてくる主薬が、消化管通過経路に沿いつつ徐々に吸収されて持続的な体液濃度を維持する方向に作用することが期待され、更に後期に至って例えば小腸の中部乃至下部に到達した錠剤中の速溶部から崩壊放出されてくる主薬は、当該消化管部位から速やかに吸収され、体液濃度を引続き高レベルに維持する方向に作用することが期待される。

本発明錠剤の内層側構成体である主薬含有速溶部は、体液と接したときに主薬を速やかに体液中へ放出することが期待される部分であって、主薬を速溶させるための製剤学的構成については、従来から採用されている技術を利用することができる。例えば主薬を崩壊剤、賦形剤、並びに当分野で一般に用いられている各種添加剤等と混合練和して顆粒とし、次いでこれを内層錠とするために打錠する方法等が例示される。ここで上記崩壊剤としては、例えば各種デンプン類（例えばトウモロコシデンプン、バレイショデンプン、コメデンプン、

1 α -デンプン、カルボキシメチルデンプン等)、ゴム類(例
 えばアラビアゴム等)、セルロース誘導体(例えばカルボキ
 シメチルセルロースカルシウム、カルボキシメチルセルロー
5 スナトリウム、低置換度ヒドロキシプロピルセルロース、架
 橋カルボキシメチルセルロースナトリウム等)、各種イオン
 交換樹脂(例えばカリウムポリメタクリレート等)等が例示
 される。また賦形剤としては、例えば乳糖、白糖、マンニッ
 ト等が例示される。例示された様な崩壊剤や賦形剤は主薬の
10 性質や目的とする持続時間等を考慮して適宜選択され、必要
 に応じて2種以上を併用することも許容される。

 主薬が水に対して不溶性もしくは極めて難溶性で消化管か
 らの吸収が不十分であると考えられる場合は、上記顆粒の形
 成に当たって天然もしくは合成の水溶性高分子物質を併用す
 ることが推奨される。これらの水溶性高分子物質の添加につ
15 いては、主薬、崩壊剤、賦形剤等と共にいっせいに、もしく
 は任意の順序で順次添加して混合練和し顆粒を形成する様に
 しても良いが、必要であれば予め主薬を水溶性高分子物質中
 に分散させて乾燥し一旦固体分散体等の易溶性剤形に導き、
 その後前記崩壊剤や賦形剤(必要であれば更に水溶性高分子
20 物質)等と混合練和して顆粒を製造することが推奨される場
 合もある。上記した水溶性高分子物質としては、まず天然の
 ものとしては例えばセルロース誘導体(例えばヒドロキシプ
 ロピルメチルセルロース、メチルセルロース、ヒドロキシプ
 ロピルセルロース、カルボキシメチルセルロース等)、或は
25 多糖類(例えばプルラン、デキストラン等)、合成のもの

1 しては例えばポリビニルピロリドン、架橋ポリビニルピロリ
 ドン、ポリエチレンオキシド等を例示することができる。こ
 れらは主薬の難溶性の程度に応じて適宜選択され、必要に応
 じて2種以上を併用することもできる。

5 顆粒製造時に使用される崩壊剤量は、特に限定されないが、
 崩壊剤の種類や主薬の性質、更には目的とする速溶性等を考
 慮して適宜定めれば良く、通常は顆粒成分全量に対して10～75
 重量%、好ましくは40～60重量%の範囲内から選択する。また
10 水溶性高分子化合物の使用量も特に限定されず主薬の水難溶
 性の程度、水溶性高分子物質の種類等を考慮して適宜定めれ
 ば良く、通常は顆粒成分全量に対して2.5～60重量%、好まし
 くは5～40重量%の範囲内から選択する。

 こうして形成された速溶性の顆粒は常法に従ってステアリ
 ン酸マグネシウム、ステアリン酸カルシウム、タルク、コー
15 ンスターチ等の滑沢剤を用いて打錠することにより本発明の
 速溶性内層部が形成される。

 次に本発明錠剤の外層側構成体である主薬含有徐放部は、
 体液と接したときに主薬を徐々に体液中へ放出することが期
 待される部分であって、主薬を徐放させるための製剤学的構
20 成については、従来から採用されている汎用の徐放化技術を
 利用することができる。例えば前記の様に内層側用として作
 製した顆粒をワックス処理に付してワックス被覆された外層
 側構成体を作成し、これを前記打錠済の速溶性内層部の外周
 を被覆する様にプレスコートすれば本発明錠剤を得ることが
25 できる。ここで用いられるワックスは水に不溶性もしくは難

1 溶性のものであり、例えば各種ロウ（例えばカルナウバロウ等）、各種硬化油（例えば大豆硬化油、ヒマシ硬化油等）、パラフィン類等が用いられ、これらは単独で用いてもよく、
5 或は2種以上を併用しても良い。

5 ワックス処理の方法は特に限定されないが、例えば上記ワックスの融液中に前記顆粒を加えて練合し、乾燥・整粒することによって徐放性顆粒が得られる。ワックスの使用量は特に限定されず、用いるワックスや主薬の性質および目的とする持続時間等によって適宜定めれば良いが通常は外層側構成体である主薬含有徐放部の全重量に対して10～70重量%、好ましくは20～60重量%の範囲内から選択する。

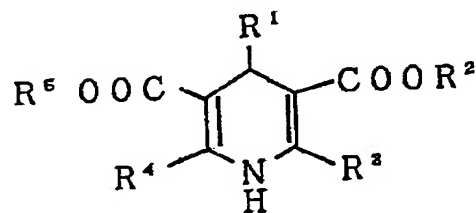
10 上記説明では、内層側構成体として作製した顆粒をワックス処理に付すことによって外層側構成体を製造すると述べた。この様な方法で製造された外層側構成体はワックス処理の部分を除いた顆粒構成が内層側のそれと全く同一になる。本発明はこの様な場合も技術的範囲に包含するが、内層側と外層側の顆粒構成を夫々の特性に合わせて別処方とすることも当然に本発明に包含される。例えば崩壊剤については内層側が速溶性を要件としていることに鑑み、外層側顆粒よりも多く
15 配合することが推奨される場合がある。但し内層側の崩壊剤含有量が多くなると、内層が大きくなり錠剤全体が大きくなって、錠剤の服用が困難になることが恐れられる。そこで錠剤全体の大きさをある程度以下の大きさにまとめることの必要から、内層側顆粒を可及的コンパクトに成形することが要求される
20 場合が生じ、この様なときは内層側処方における添加剤、例
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1 えば水溶性高分子物質量を外層側顆粒のそれよりも、必要且
つ可能な限度で少なくすることができ、例えば、外層側にお
ける水溶性高分子物質量を100重量部としたとき内層側におけ
る水溶性高分子物質を15～40重量%、好ましくは25～35重量%
5 とすることが推奨される。或は錠剤製造における汎用添加剤
である乳剤等の賦形剤を内層側処方から減少または削除する
様な工夫を行なうことも有意義である。

 ワックス処理を行なうに当たっては、ワックスによる徐放
性を更に微細に制御する目的で、或はワックスの崩壊性を安
定した速度で進行させる目的で、他の成分を併用する場合が
10 ある。そのような第3成分としては例えばエチルセルロース
が例示される。エチルセルロースはエチル基の置換度によっ
てその化学的性質（例えば水溶性や粘度）が変化するので、
添加目的に合わせて最適の置換度のものを選択することが推
奨される。一般には粘度を指標とし、7～10 cps の範囲の粘
15 度を有するものを選択して使用するのが望ましい。またエチ
ルセルロースの配合量はその粘度や配合目的、或はワックス
の種類を考慮して定めるが、通常はワックスの使用量に対し
て0.75～2.5（重量比）、好ましくは0.8～1.5（重量比）の範
20 囲から選択される。尚エチルセルロースの使用に当たっては、
後述の実施例に示す様に、ワックス処理前の主薬含有顆粒（外
層用固体分散体）とエチルセルロースを十分に混合させた状
態でワックス処理させる方法が推奨されるが、上記以外に、
エチルセルロースとワックスを十分に混合融解させた状態で
25 主薬含有顆粒に被覆させたり、使用予定量のワックス及びエ

1 チルセルロースを夫々二分して前記の各方法を組合わせて行
う方法などが自由に採用される。こうして形成された外層部
顆粒を用いて前記内層部錠の外周にプレスコートすれば本発
明の持続性製剤が得られる。

5 本発明の持続性製剤を製造するのに適した主薬は、経口投
与に好適と考えられる薬物、または持続性さえ実現されるな
らば経口剤とすることが期待される様な薬物が全てその対象
となる。従って循環器系薬剤、消化管系薬剤、呼吸器系薬剤、
中枢神経系薬剤、自律神経系薬剤、ホルモン剤、抗生物質、
10 その他各種化学療法剤等が広く本発明の適用対象となる。中
でも循環器系薬剤は例えば起床時に多いとされる心臓発作を
予防するという観点から持続性薬剤の開発が強く望まれてお
り、本発明の適用は特に有意義である。この様な循環器系薬
剤は特に限定されないが、代表的なものとしては例えば下記
15 の一般式で示されるようなジヒドロピリジン化合物が示され
る。



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25 [式中、R¹はハロゲン、ニトロ及びトリハロ（低級）アルキ
ルによって置換されていてもよいフェニル基、R²は低級アル
キル基または低級アルコキシ（低級）アルキル基、R³はシア

1 ノ基、低級アルキル基またはアミノ（低級）アルコキシ（低級）アルキル基、 R^4 は低級アルキル基、 R^5 は低級アルキル基、
N-低級アルキル-N-アル（低級）アルキルアミノ（低級）アルキル基または低級アルコキシ（低級）アルキル基を意味
5 する]

R^1 の好適な例としては2-クロロフェニル、2, 3-ジクロロフェニル、2-ニトロフェニル、3-ニトロフェニル、トリフルオロメチルフェニル等が挙げられる。

10 R^2 の好適な例としてはメチル、エチル、プロピル、2-プロポキシエチル等が挙げられる。

R^3 の好適な例としてはメチル、2-アミノエトキシメチル等が挙げられる。

R^4 の好適な例としてはメチル等が挙げられる。

15 R^5 の好適な例としてはメチル、エチル、イソプロピル、イソブチル、2-プロポキシエチル、2-(N-メチル-N-ベンジルアミノ)エチル等が挙げられる。

20 上記一般式で示されるジヒドロピリジン化合物の好適な例としては、例えばニフェジピン、ニカルジピン、ニモジピン、ニソルジピン、ニトレンジピン、アムロジピン、フェロジピン、ニルジピンまたはニルバジピンが挙げられ、それらの中でも最も好ましいものは、ニルバジピンである。

25 また上記一般式で示される化合物以外にマニジピン、ベニジピン、ダロジピン、イスラジピン等のジヒドロピリジン化合物もまた、本発明の好ましい主薬として例示することができる。

- 1 ニルバジピンを主薬として含有する持続性薬剤の処方例および製造例を示す。

処方A

内層錠（固体分散体処方）

5	ニルバジピン	4mg
	HPMC 2910	12mg
	（ヒドロキシプロピルメチルセルロース）	
	L-HPC	33.8mg
	（低置換度ヒドロキシプロピルセルロース）	
10	ステアリン酸マグネシウム	0.2mg
	（小計）	50mg

外層

	ニルバジピン	8mg
	HPMC 2910	40mg
15	L-HPC	45mg
	乳糖	57mg
	大豆硬化油	150mg
	ステアリン酸マグネシウム	0.6mg
	（小計）	300.6mg
20	（合計）	350.6mg

処方B

内層錠（固体分散体処方）

	ニルバジピン	4mg
	HPMC 2910	12mg
25	L-HPC	33.8mg

1	ステアリン酸マグネシウム	0.2mg
	(小計)	50mg
	外層	
	ニルバジピン	8mg
5	H P M C 2910	40mg
	L - H P C	45mg
	乳糖	57mg
	大豆硬化油	78mg
	エチルセルロース	82mg
10	ステアリン酸マグネシウム	0.6mg
	(小計)	310.6mg
	(合計)	360.6mg

処方 C

内層錠 (固体分散体処方)

15	ニルバジピン	4mg
	H P M C 2910	12mg
	L - H P C	19mg
	ステアリン酸マグネシウム	0.14mg
	(小計)	35.14mg
20	外層	
	ニルバジピン	8mg
	H P M C 2910	40mg
	L - H P C	25mg
	乳糖	20mg
25	大豆硬化油	57.9mg

1	エチルセルロース	60.8mg
	ステアリン酸マグネシウム	0.41mg
	(小計)	212.11mg
	(合計)	247.25mg

5 製造例 1 (処方 A, B の内層錠の製造)

60℃の温浴中でエタノール(660ml)にニルバジピン(24g)を溶解させ、40℃まで冷却しておく。一方HPMC 2910(72g)とL-HPC(202.8g)を十分混合し、この混合物中に、先に得た40℃のニルバジピン溶液を加え、10分間練合した後、真空乾燥した。得られた乾燥物を粉碎・整粒し、ステアリン酸マグネシウム(1.2g)を添加して混合した後、混合物を打錠機で打錠し、内層錠を製造した。

製造例 2 (処方 A, B の外層用固体分散体粒の製造)

60℃の温浴中でエタノール(1320ml)にニルバジピン(48g)を溶解させ、40℃まで冷却しておく。一方HPMC 2910(240g), L-HPC(270g)および乳糖(342g)の混合物を準備しておき、これに先に得た40℃のニルバジピン溶液を加え、10分間練合した後真空乾燥した。得られた乾燥物を粉碎・整粒し、外層用の固形分散体を製造した。

20 製造例 3 (処方 C の内層錠の製造)

60℃の温浴中でエタノール(660ml)にニルバジピン(24g)を溶解させ、40℃まで冷却しておく。一方HPMC 2910(72g)とL-HPC(114g)を十分混合し、この混合物中に、先に得た40℃のニルバジピン溶液を加え、10分間練合した後、真空乾燥した。得られた乾燥物を粉碎・整粒し、ステアリン酸マ

1 グネシウム (0.84 g) を添加して混合した後、混合物を打錠機
 で打錠し、内層錠を製造した。

製造例 4 (処方 C の外層用固体分散体粒の製造)

 60℃の温浴中でエタノール (1320ml) にニルバジピン (48 g)
5 を溶解させ、40℃まで冷却しておく。一方 H P M C 2910
 (240 g) , L - H P C (150 g) および乳糖 (120 g) の混合
 物を準備しておき、これに先に得た40℃のニルバジピン溶液を
 加え、10分間練合した後真空乾燥した。得られた乾燥物を粉碎・
 整粒し、外層用の固形分散体を製造した。

10 製造例 5 (処方 A の外層固体分散体を用いた外層部用顆粒の
 製造)

 大豆硬化油 (900g) を80℃で融解し、これに処方 A の外層固
 体分散体 (900g) を加え、80℃で融解させながら造粒する。こ
 れを室温まで放冷した後、整粒した。

15 製造例 6 (処方 B の外層固体分散体を用いた外層部用顆粒の
 製造)

 大豆硬化油 (468g) を80℃で融解し、これにエチルセルロー
 ス (粘度45cps , 492g) 及び処方 B の外層固体分散体 (900g)
 の混合物を加え、80℃で融解させながら造粒する。これを室温
20 まで放冷した後整粒した。

製造例 7 (処方 C の外層固体分散体を用いた外層部用顆粒の
 製造)

 大豆硬化油 (900 g) を80℃で融解し、これに処方 C の外層
 固体分散体 (1446 g) を加え、80℃で融解させながら造粒する。
25 これを室温まで放冷した後、整粒した。

1 製造例 8 (2 層錠の製造)

製造例 1 ~ 3 で製造した内層錠の外周に、製造例 5 ~ 7 で得た外層部用顆粒をプレスコートし、本発明の持続性製剤である二層錠 A, B, C (処方は前掲の通り) を得た。

5 比較製造例 1 (ニルバジピン含有普通錠の製造)

下記処方に従ってニルバジピン含有普通錠を製造した。

	ニルバジピン	2mg
	H P M C	10mg
	L - H P C	30mg
10	乳糖	137.5mg
	ステアリン酸マグネシウム	0.5mg
	(合計)	180mg

実験例 1

本発明の処方 A からなる二層錠 A と比較普通錠に対し、第 12 改正日本薬局方の第 II 法 (パドル法) に従って 200rpm, 900ml (第 1 液: pH1.2) を用いて in vitro の溶出試験を行った。結果は第 1 図に示す通りであって、比較普通錠 (●印) は各時間の測定値 (各プロット) が全て 100 % を超えており、短時間のうちに速放されてしまっているが、本発明の二層錠 A (○印) では 7 時間目まではほぼ時間経過に比例した溶出率を示しており、優れた徐放性を示していることが分かる。

実験例 2

実験例 1 において用いた回転数条件および溶出液条件のいずれか一方を変更して本発明の二層錠 A, B について in vitro の溶出試験を行った。第 2 図の (A-1), (A-2) は二

- 1 層錠Aの結果、図2の(B-1), (B-2)は二層錠Bの
結果を夫々記す。尚(A-1), (B-1)では第1液を用
いて回転数を変え、(A-2), (B-2)では回転数を200rpm
に固定して溶出液を変えた。図に見られる通り、本発明の二
5 層錠A, Bはいずれも優れた徐放性を示したが、外層部にエ
チルセルロースを併用した二層錠Bの徐放性は極めて安定し
たものと言うことができる。

実験例3

- 二層錠Cについて実験例2と同様の溶出試験を行った。結
10 果は第3図に示す通りであり、第一液(●印)、pH6.5緩衝
液(○印)、蒸留水(△印)のいずれの場合も安定した徐放
性を示すことが分かる。

実験例4 (犬を用いたin vivo の経口吸収性評価)

- 体重約10kgの雄性ビーグル犬6頭を用い普通錠については実
15 験日前日より絶食させ、2mg×3錠を経口投与し、直後に経口
用ゾンデで30mlの水を強制投与した。二層錠Aについては実験
日前日より絶食させ、二層錠A投与30分前に犬用固形飼料100g
を与え、1錠経口投与し、以下同様に処置した。各投与後、
各時間経過毎に前腕静脈より約3mlの血液を採取し局方ヘパリン
20 ン10μl (5000単位)を添加した。ガスクロマトグラフでニル
バジピンの血漿中濃度を測定したところ第4図の様な結果が
得られた。本発明の二層錠Aは優れた徐放性を示し、しかも
相当長時間に亘って高い血中濃度を維持していることが分か
る。

- 25 産業上の利用可能性

1 本発明の持続性製剤は上記の様に構成されており、外層中
の主薬は徐々に放出されて優れた長時間持続性を示し、しか
も内層中の主薬が放出される時点では該内層中の主薬が速や
かに放出されるので、引続き高いレベルの血中濃度が維持さ
5 れ、治療上及び予防上の有効血中濃度持続時間が極めて遷延
されることとなった。

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請求の範囲

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1. 主薬を含有する速溶部によって内層を構成すると共に、
該主薬と同一又は類似薬効の主薬を含有する徐放部によって
外層を構成したものであることを特徴とする持続性製剤。

2. 内層の速溶部および外層の徐放部に含有される主薬が
いずれも冠血管および／または末梢血管の拡張作用物質であ
る請求項 1 記載の持続性製剤。

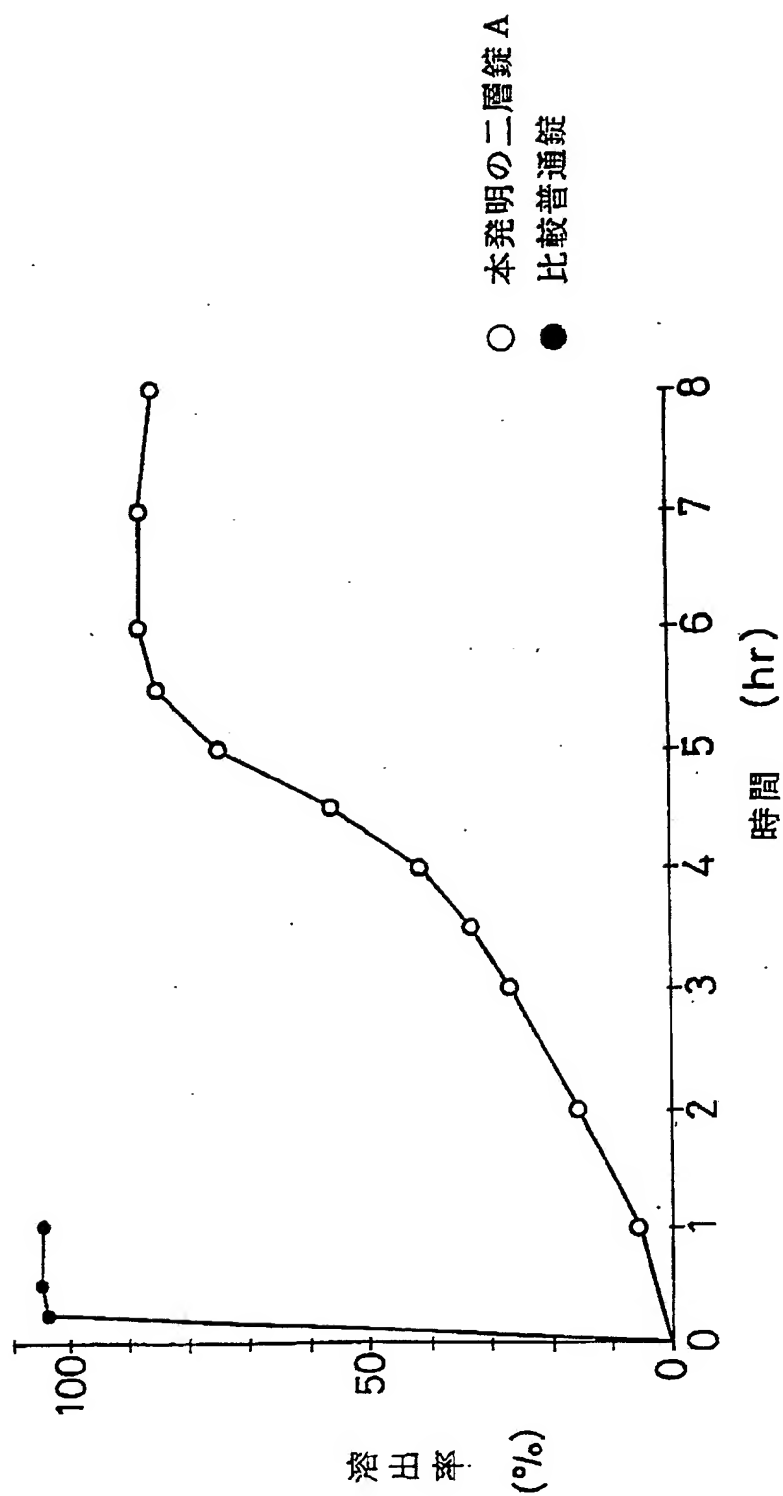
3. 主薬がジヒドロピリジン化合物である請求項 2 記載の
持続性製剤。

4. 主薬がニルバジピンである請求項 3 記載の持続性製剤。

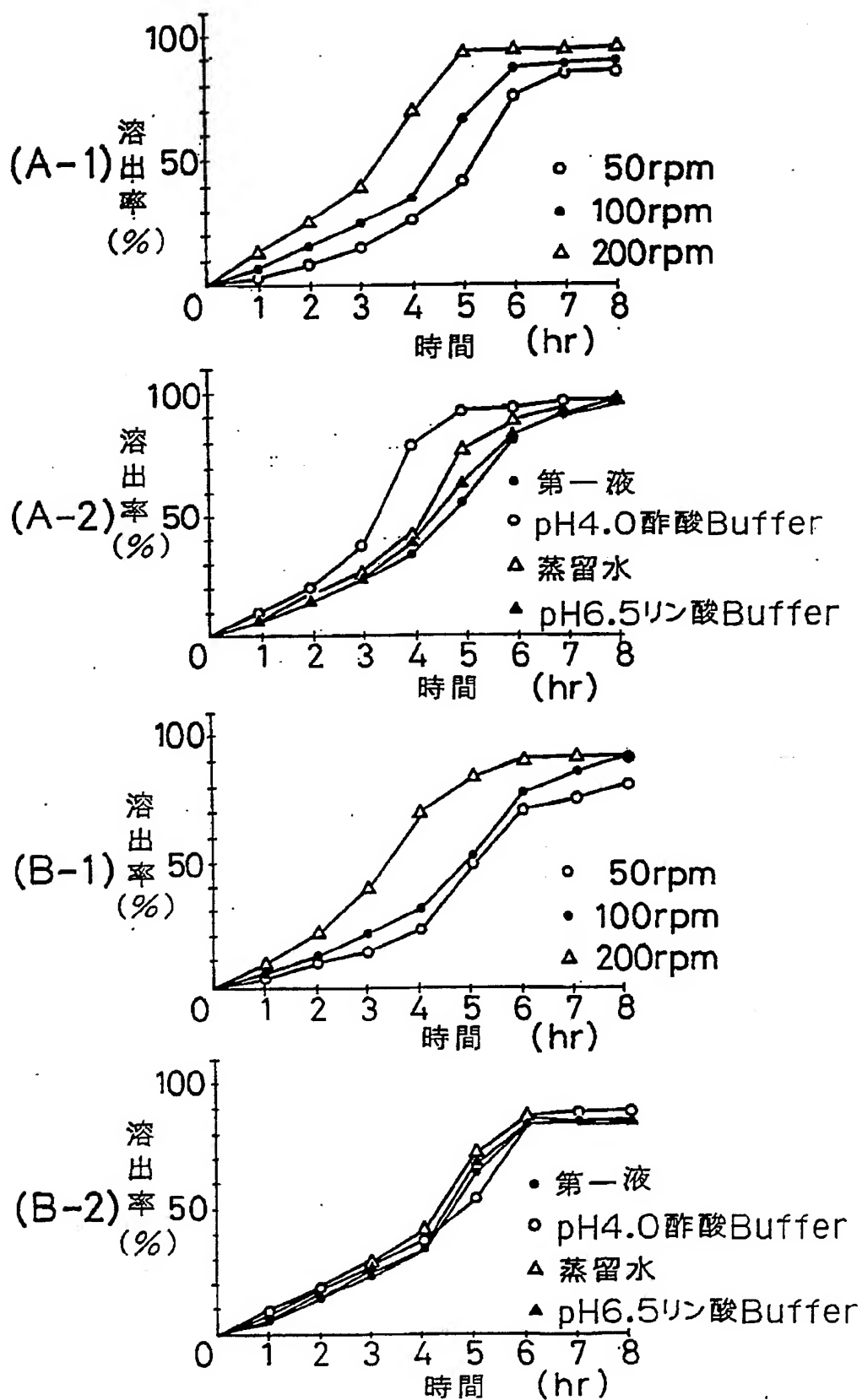
5. 速溶部が、主薬およびヒドロキシプロピルメチルセル
ロースを含有する易溶性固形体で構成され、徐放部が、主薬
を含有する崩壊性の顆粒及びワックス類から構成された徐放
性固形体で構成されたものである請求項 1～4 のいずれかに
記載の持続性製剤。

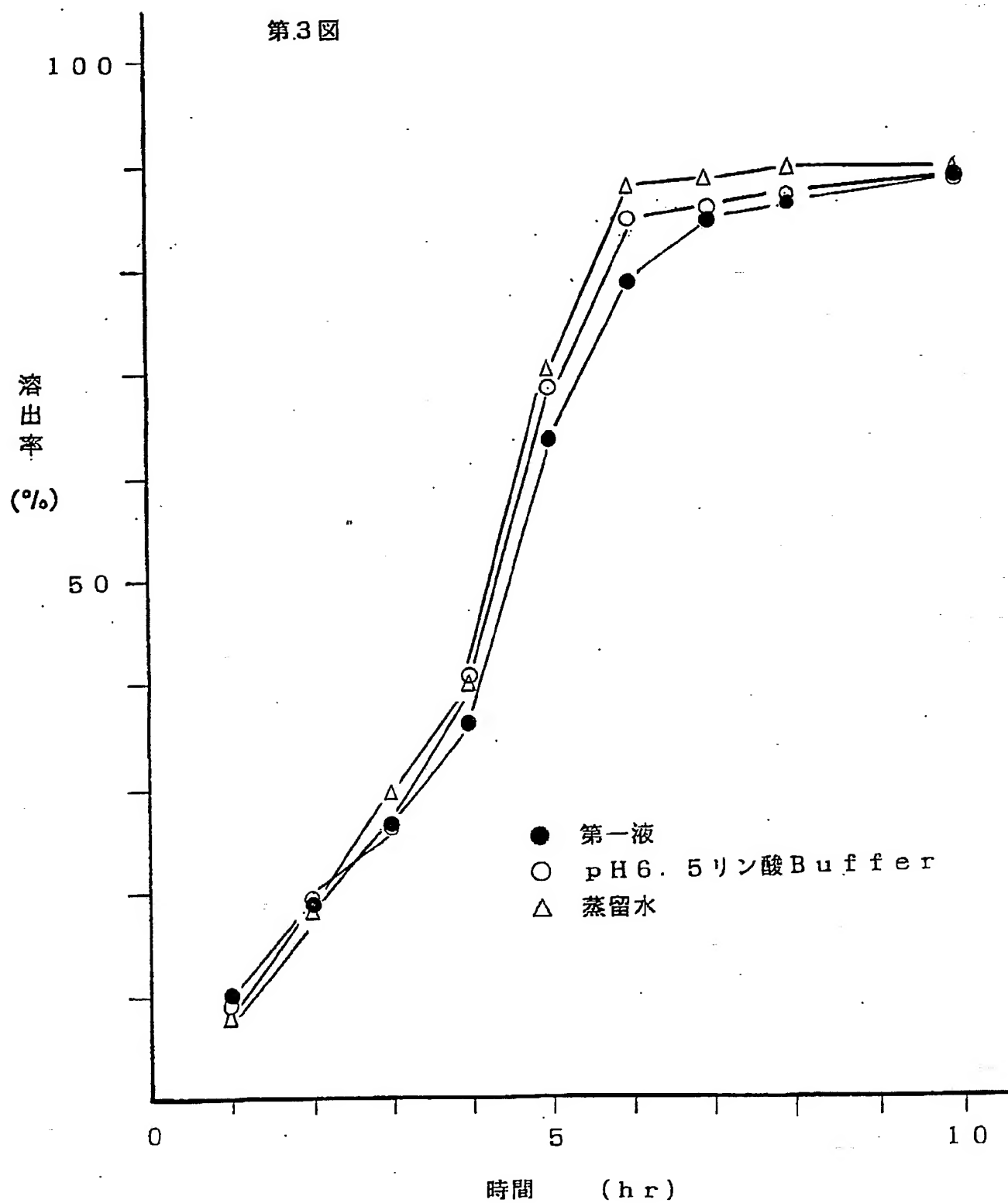
6. 速溶部におけるヒドロキシプロピルメチルセルロース
の含有量が速溶部中の主薬に対して 3～7 倍（重量比）であ
り、徐放部における崩壊剤の含有量が顆粒全成分中 10～60 重量
％であり、且つ徐放部におけるワックスの含有量が徐放部全
成分中 20～65 重量％である請求項 5 記載の持続性製剤。

第1図

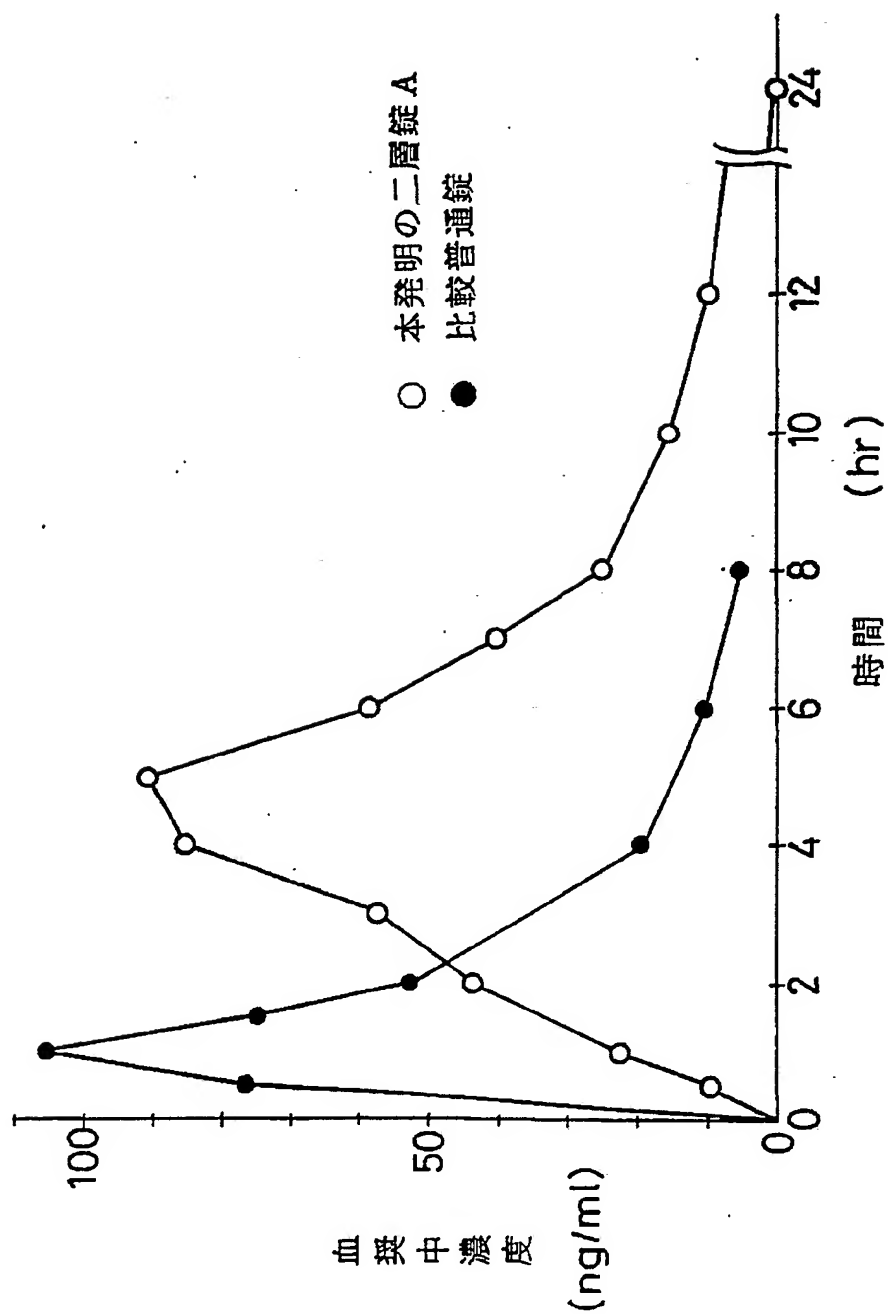


第2図





第4図



INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/01183

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC <div style="margin-top: 10px;">Int. Cl⁵ A61K9/28</div>											
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched ⁷</div> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width: 25%; padding: 5px;">Classification System</th> <th style="padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; padding: 10px;">IPC</td> <td style="padding: 10px;">A61K9/20-9/42, 31/44</td> </tr> </table> <div style="text-align: center; margin-top: 10px; font-size: small;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC	A61K9/20-9/42, 31/44					
Classification System	Classification Symbols										
IPC	A61K9/20-9/42, 31/44										
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; padding: 5px;">Category *</th> <th style="width: 60%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 10px;">X</td> <td style="padding: 10px;">JP, A, 61-172813 (Japan Atomic Energy Research Institute), August 4, 1986 (04. 08. 86), Line 8, upper left column to column 7, upper right column, page 2, lines 3 to 16, upper right column, page 4, line 17, lower left column to line 10, lower right column, page 5 (Family: none)</td> <td style="text-align: center; vertical-align: top; padding: 10px;">1, 2</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 10px;">Y</td> <td style="padding: 10px;">JP, A, 62-246512 (Fujisawa Pharmaceutical Co., Ltd.), October 27, 1987 (27. 10. 87), Lines 5 to 8, lower left column, page 1, lines 5 to 15, lower left column, lines 9 to 12, lower right column, page 2, lines 4 to 7, lower left column, line 7 to last line, lower right column, page 3 (Family: none)</td> <td style="text-align: center; vertical-align: top; padding: 10px;">1-6</td> </tr> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	JP, A, 61-172813 (Japan Atomic Energy Research Institute), August 4, 1986 (04. 08. 86), Line 8, upper left column to column 7, upper right column, page 2, lines 3 to 16, upper right column, page 4, line 17, lower left column to line 10, lower right column, page 5 (Family: none)	1, 2	Y	JP, A, 62-246512 (Fujisawa Pharmaceutical Co., Ltd.), October 27, 1987 (27. 10. 87), Lines 5 to 8, lower left column, page 1, lines 5 to 15, lower left column, lines 9 to 12, lower right column, page 2, lines 4 to 7, lower left column, line 7 to last line, lower right column, page 3 (Family: none)	1-6
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X	JP, A, 61-172813 (Japan Atomic Energy Research Institute), August 4, 1986 (04. 08. 86), Line 8, upper left column to column 7, upper right column, page 2, lines 3 to 16, upper right column, page 4, line 17, lower left column to line 10, lower right column, page 5 (Family: none)	1, 2									
Y	JP, A, 62-246512 (Fujisawa Pharmaceutical Co., Ltd.), October 27, 1987 (27. 10. 87), Lines 5 to 8, lower left column, page 1, lines 5 to 15, lower left column, lines 9 to 12, lower right column, page 2, lines 4 to 7, lower left column, line 7 to last line, lower right column, page 3 (Family: none)	1-6									
<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>											
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="margin-top: 10px;">November 17, 1992 (17. 11. 92)</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="margin-top: 10px;">December 8, 1992 (08. 12. 92)</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="margin-top: 10px;">Japanese Patent Office</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="height: 40px;"></div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="margin-top: 10px;">November 17, 1992 (17. 11. 92)</div>	Date of Mailing of this International Search Report <div style="margin-top: 10px;">December 8, 1992 (08. 12. 92)</div>	International Searching Authority <div style="margin-top: 10px;">Japanese Patent Office</div>	Signature of Authorized Officer <div style="height: 40px;"></div>					
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International Searching Authority <div style="margin-top: 10px;">Japanese Patent Office</div>	Signature of Authorized Officer <div style="height: 40px;"></div>										

I. 発明の属する分野の分類		
国際特許分類 (IPC) Int. Cl⁵ A 61 K 9 / 2 8		
II. 国際調査を行った分野		
調 査 を 行 っ た 最 小 限 資 料		
分 類 体 系	分 類 記 号	
I P C	A 61 K 9 / 2 0 - 9 / 4 2 , 3 1 / 4 4	
最小限資料以外の資料で調査を行ったもの		
III. 関連する技術に関する文献		
引用文献の カテゴリー ※	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	請求の範囲の番号
X	JP, A, 61-172813 (日本原子力研究所), 4. 8月. 1986 (04. 08. 86), 第2頁左上欄第8行-右上欄第7欄, 第4頁右上欄第3 -16行, 第5頁左下欄第17行-右下欄第10行, (ファミリーなし)	1, 2
Y	JP, A, 62-246512 (藤沢薬品工業株式会社), 27. 10月. 1987 (27. 10. 87), 第1頁左下欄第5-8行, 第2頁左下欄第5-15行, 右下欄第9-12行, 第3頁左下欄第4-7行, 右下欄 第7-末行, (ファミリーなし)	1-6
※引用文献のカテゴリー 「A」 特に関連のある文献ではなく、一般的技术水準を示すもの 「E」 先行文献ではあるが、国際出願日以後に公表されたもの 「L」 優先権主張に疑義を提起する文献又は他の文献の発行日 若しくは他の特別な理由を確立するために引用する文献 (理由を付す) 「O」 口頭による開示、使用、展示等に言及する文献 「P」 国際出願日前で、かつ優先権の主張の基礎となる出願の 日の後に公表された文献 「T」 国際出願日又は優先日の後に公表された文献であって出 願と矛盾するものではなく、発明の原理又は理論の理解 のために引用するもの 「X」 特に関連のある文献であって、当該文献のみで発明の新 規性又は進歩性がないと考えられるもの 「Y」 特に関連のある文献であって、当該文献と他の1以上の 文献との、当業者にとって自明である組合せによって進 歩性がないと考えられるもの 「&」 同一パテントファミリーの文献		
IV. 認 証		
国際調査を完了した日	国際調査報告の発送日	
17. 11. 92	08.12.92	
国際調査機関	権限のある職員	4 C 7 3 2 9
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 9/22, 31/44	A1	(11) International Publication Number: WO 94/00112 (43) International Publication Date: 6 January 1994 (06.01.94)
(21) International Application Number: PCT/SE93/00521 (22) International Filing Date: 11 June 1993 (11.06.93) (30) Priority data: 9201930-6 24 June 1992 (24.06.92) SE (71) Applicant: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors: FALK, Karl-Erik, Lennart ; Odonvägen 57, S-437 00 Lindome (SE). SJÖGREN, John, Albert ; Hönekullavägen 47 H, S-435 44 Mönlycke (SE). (74) Agent: LINDEROTH, Margareta; AB Astra, Patent Department, S-151 85 Södertälje (SE).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL TREATMENT AS WELL AS A PROCESS THEREOF AND THE USE (57) Abstract An oral formulation with extended release for treatment of infections in the upper gastrointestinal tract as well as processes for the preparation and the use thereof.		

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AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL
TREATMENT AS WELL AS A PROCESS THEREOF AND THE
USE

5 Technical field

The invention relates to formulations for treatment of infections in the upper gastrointestinal tract especially infections caused by *Helicobacter pylori*, and a process for the manufacture of said formulations as well as the use thereof.

10

Said formulations give a prolonged release of antimicrobial agent(s) in the upper gastrointestinal tract.

Background of the invention

15 *Helicobacter pylori* (*H.pylori*) is a recently discovered bacterium, cultured for the first time in Australia 1982 [Warren JR Lancet 1983;1:1273], which has attracted much interest due to its possible aetiological role in a number of disorders in the upper gastrointestinal tract. It is considered a major cause in the
20 development of peptic ulcer disease [*Helicobacter pylori* Working Party Report. World Congress in Gastroenterology, Sydney 1990] *H. pylori* is accepted as the aetiological agent in most cases of chronic non-specific gastritis. Chronic active gastritis is highly correlated to *H. pylori*-infections. The organism is found in
25 association with chronic active gastritis in almost 100% of the cases. Further, it was concluded in a case-control study of 372 patients that infection with *H. pylori* is associated with an increased risk of gastric adenocarcinoma and may be a cofactor in the pathogenesis of this malignant condition [Parsonnet J,
30 Friedman GD, Daniel MS et al. N Engl J Med 1991;325:1127-31].

The pathogenic mechanism of *H. pylori* is not yet known in its

details. The mode of transmission is unknown but considered to be by the faecal oral route and may be waterborne. *H. pylori* is found throughout the world but there is a higher prevalence of the organism in less developed countries and in patients with low economic status in western countries. The overall prevalence in western countries is about 52 % and increases with advancing age.

H. pylori is a Gram-negative microaerophilic bacterium which is about 3.5 μm in length and 1 μm in diameter. Due to the presence of 4-6 flagella attached to the end of its typical S- or spiral shape form, the bacterium can move rapidly in mucus. It lives closely attached to the gastric epithelial cells beneath the mucus layer and colonises the stomach, mainly the antrum, in a patchy fashion.

In vitro studies show a high sensitivity of *H. pylori* to many antibiotics [McNulty CA, Dent JC. Eur J Clin Microbiol Infect Dis 1988;7:566-569], [Lambert T, Megraud F, Gerbaud G et al. Antimicrob Agents Chemother 1986;30:510-511]. However, in vivo studies have demonstrated that there is a small correlation between in vitro sensitivity for *H. pylori* and treatment results in vivo for antibacterial drugs. The eradication regime with best eradication results today (elimination of *H. pylori* in 80-90% of treated patients) is triple therapy [Axon ATR. Scand J Gastroenterol 1989;24(suppl 160) :35-38.]. The therapy is a combination of a bismuth preparation, metronidazole and amoxicillin or tetracycline. However, the dosage regimen involves many tablets and there is a need of administration several times per day. This is difficult for the patient to follow and compliance has been shown to be important to achieve the high eradication

rates. Adverse effects, mainly due to metronidazole or bismuth are very common. About 30% of the patients have reported side effects [Axon ATR, Scand J Gastroenterol 1989;24(suppl 160):35-38].

5

Monotherapy of different antibiotics which are known to have good effect in vitro against *H.pylori* is insufficiently effective in vivo. Amoxicillin, for example, eradicates *H.pylori* only in about 20% of treated patients. Combination of two drugs give higher eradication rates than monotherapy. Bismuth preparations (bismuth subsalicylate or colloidal bismuth subcitrate) in combination with amoxicillin eradicated *H.pylori* in 44 % of treated patients, bismuth + metronidazole, amoxicillin + tinidazole and amoxicillin + metronidazole in about 55 % of the patients, respectively [Chiba N, Rademaker JW, Rao BV et al. Gut 1991;32:A1220-1221 Abstract].

Antibacterial agents have also been combined with acid secretion inhibitors. Combinations with histamin₂-blockers show no improved effect. Proton pump inhibitors e g omeprazole, which have very little anti-*H.pylori* effect on its own show a synergistic effect in combination with antibiotics. A dose of 750 mg amoxicillin twice daily with 40 mg omeprazole once daily was reported to eradicate *H.pylori* in 54% of the patients [Unge P, Eriksson K, Bergman B. et al. Gastroenterol 1992;102(4);A183(abstract)]. Any explanation for this synergistic effect is not yet known, according to available information.

Many antibiotics have relatively short duration of action and are given 3-4 times a day. Attempts to prolong the action by use of prolonged release products have generally been unsuccessful

because the absorption of the antibiotic from the gastrointestinal tract is poor when administered in slow release form [Delgado Charro MB, Vila Jato JL. Int J Pharm 1992;78;35-41] Instead antibiotics are given in rapidly absorbed formulations, e g tablets or capsules. In order to achieve sufficiently long duration of action higher doses are given.

In all previous studies on H.pylori eradication rapidly available dosage forms of the antibacterial agents have been used and attempts have been made to increase the success rate by using very high doses of antibacterials as well as proton pump inhibitors. For example, 82% of treated patients were eradicated after 10 days therapy of 40 mg omeprazole twice daily in combination with 1 g amoxicillin twice daily followed by 6 weeks monotherapy of 20 mg omeprazole once daily.[Bayerdörffer E, Mannes GA, Sommer A et al. Gastroenterol 1992;102(4):A38(abstract)].

Outline of the invention

We have discovered that the effectiveness of the treatment can be improved in an entirely different way, namely by administration of the antibacterial agents in prolonged release formulations and administer the formulations in such a way that they stay in the stomach several hours. It is not yet known if the H.pylori bacterias are accessible for treatment by antibacterial agents in the stomach or if the drug has to be absorbed and reach the bacterias via the blood circulation. The improved effect of formulations according to this invention may indicate that a local effect in the stomach is important.

Examples of formulations with prolonged gastric residence time

are bioadhesive systems which interact with mucus or the mucosa. Another way to prolong the residence time is swelling systems which expand in contact with the gastric fluid to a size which does not allow the system to pass through the pylorus.

- 5 Further examples are formulations with very high density or systems which float on the gastric contents. It has also been observed that large non-disintegrating tablets or capsules can be retained for several hours in the stomach. The retention time in the stomach is especially prolonged when the tablet or capsule is
10 administered together with food due to the sieving function of pylorus when the stomach is in the digestive mode [Davis SS, Hardy JG, Taylor MJ et al. Int J Pharm 1984;21:331-340]. Food also retards the emptying of tablets or pellets, but the effect is less pronounced. The critical size is reported to be about 7 mm
15 [Khosla R. Nottingham: University of Nottingham, 1987.(Diss).]

- The drug should be released within 1-24 h, preferably 1-6 h. To achieve an effective treatment of H.pylori infection the product should remain in the stomach at least 2-4 h, preferably more than
20 6 h. The major part of the drug should be released before the tablet leaves the stomach. The drugs suitable for the preparations according to the invention are e.g. ampicillin, amoxicillin, benzylpenicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin,
25 methicillin, oxacillin, piperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalixin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin,
30 dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin,

tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be preferable, for example to minimize the risk for developing resistance. The antimicrobial agents can also be combined with other drugs used in the treatment of acid related diseases e.g. acid pump inhibitors or H₂-blockers, such as for example omeprazole.

Possible formulations to be used are large non-disintegrating tablets or capsules e.g. inert matrix tablets [Hui H, Robinson JR, Lee VHL. Design and fabrication of Oral Controlled Delivery Systems. In: Robinson JR, Lee VHL, eds. Controlled Drug Delivery. Fundamentals and applications. New York: Marcel Dekker, Inc, 1987:373-432], osmotic pumps [Davis SS, Fara JW. Osmotic pumps. In: Hardy JG, Davis SS, Wilson CG, eds. Drug Delivery to the Gastrointestinal Tract. Chichester: Ellis Horwood Limited, 1989:97-109.] and membrane-coated tablets. Further, swelling systems [Banker, US Patent + no 261,242,] floating systems [Davis SS, Stockwell AF, Taylor MJ et al. Pharm Res 1986;3:208-213.], [Washington N, Wilson CG, Greaves JL et al. Scand J Gastroenterol 1988;23:920-924], formulations with high

density [Devereux JE, Newton JM, Short MB. J Pharm Pharmacol 1990;42:500-501] and mucoadhesive systems [Junginger HE. Pharm Ind 1991;53:1056-1065] prepared from e.g. polycarbophil, polyacrylic acid, methylcellulose, polyethylene oxide, chitosan, tragacanth, sodium carboxymethyl cellulose can
5 be used.

An example from the above listed formulations is the inert porous matrix tablet which is obtained by mixing the drug with waxes or
10 water insoluble polymers and with fillers and binders. Paraffin, polyvinylchloride, ethylcellulose, stearyl alcohol, cetyl alcohol, carnauba wax, polyethylene, polyvinyl acetate, polymethyl methacrylate could be used as suitable diffusion retarding compounds. Other excipients used in the preparations of such
15 tablets are e.g. lactose, mannitol, calcium phosphates, magnesium stearate, hydroxypropyl methylcellulose, methylcellulose, polyvinylpyrrolidone, aluminium silicate, sodium carbonate, potassium phosphate or other suitable materials.

Examples

It is the object of the present invention to provide an extended-release preparation with prolonged gastric residence time after oral administration, containing one or more antimicrobial agents.

5

Example 1:

g

Amoxicillin sodium

830

Paraffin

500

10 Ethylcellulose

60

Magnesium stearate

28.8

Amoxicillin sodium was mixed in a planetary mixer for 5 minutes with paraffin. The resultant mixture was then moistened for 5 minutes with a solution of ethylcellulose in isopropanol and dried. The granulate was milled through a 1.0 mm sieve and lubricated for 2 minutes with magnesium stearate.

15

The granulate was compressed to tablets on a tableting machine fitted with 13 mm punches. Each tablet contained 415 mg amoxicillin sodium. The release profile of the drug is shown in Figure 1.

20

Example 2:

g

25

Amoxicillin trihydrate

215.6

Paraffin

250

Sodium carbonate

209

Ethylcellulose

30

30 Magnesium stearate

14.1

The composition according to Example 2 was formed to modified release tablets containing 375 mg of amoxicillin/tablet. The tablet were prepared in the following way:

- 5 Amoxicillin trihydrate, paraffin and sodium carbonate were mixed for 5 minutes in a planetary mixer. The remaining process was made according to Example 1. The release profile of the drug is shown in Figure 2.

10	Example 3	g
	Amoxicillin trihydrate	215
	Tripotassium phosphate	209
	Polyvinylpyrrolidone	20
15	Magnesium stearate	20

- Compressed into tablets after granulation and drying as in Example 1. The tablets were coated with a porous membrane coating consisting of polyvinyl chloride in acetone according to
- 20 [Källstrand G, Ekman B. J Pharm Sci 1983;72(7):772-775].
- Micronized sucrose (particle size less than 10 μ m) was suspended in the polymer solution. Coating was achieved by spraying the suspension on a moving bed of tablets with an airless sprayer. Coating was continued until the weight of the coat on each tablet
- 25 was 50 mg.

Example 4:

g

	Amoxicillin trihydrate	244
	Ethylcellulose	268
5	Chitosan	366
	Hydrochloric acid	0,13
	Water purified*	q.s.
	Ethanol*	q.s.

- 10 *Used in the manufacture of pellets but removed during subsequent processing

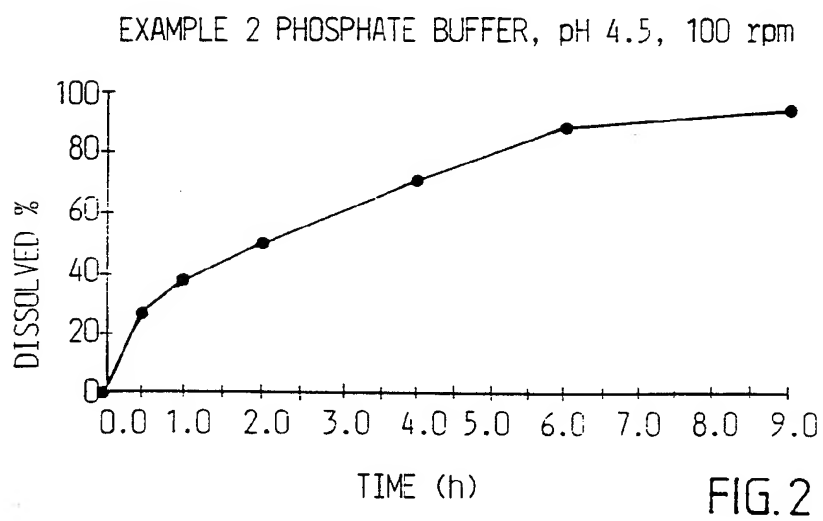
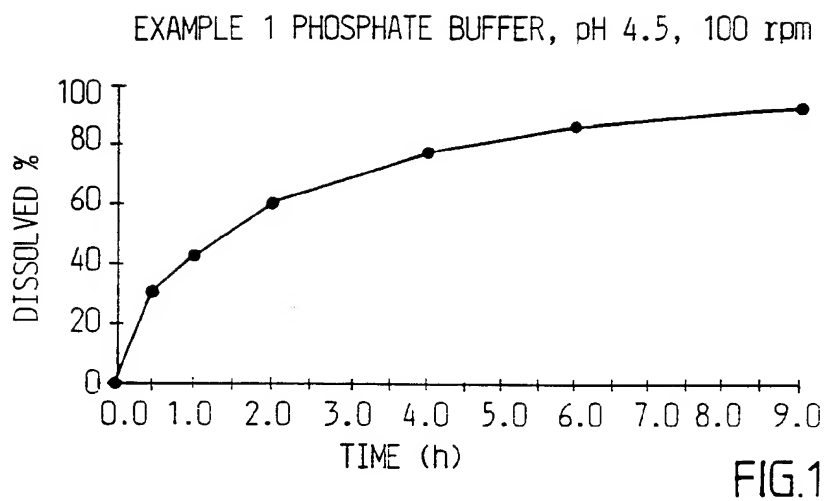
15 The bioadhesive pellets were manufactured using conventional fluid-bed coating technology. Amoxicillin trihydrate was successively coated with solutions containing chitosan and ethylcellulose, respectively.

Claims

1. An oral formulation containing active materials for treatment of infections in the upper gastrointestinal tract characterized in
5 that the formulation is retained in the stomach for a prolonged time whereby the active materials are released continuously during said time.
2. A formulation according to claim 1 where the preferred
10 retention time is at least 1 h during which period the active materials are released continuously.
3. A formulation according to claim 1, wherein the formulation
15 contains one or more antibacterial agents.
4. A formulation according to claim 1 where the infection is
caused by *Helicobacter pylori*.
5. A formulation according to claim 1 wherein the active
20 substance is amoxicillin.
6. A formulation according to claim 1 comprising a combination
of two or more active agents.
- 25 7. A formulation according to claim 1 where the dosage form has bioadhesive properties.
8. A formulation according to claim 1 consisting of a non-
30 disintegrating prolonged release formulation containing antibacterial agents.

9. A formulation according to claim 8 wherein the size is not less than 7 mm.
10. A formulation according to claim 9 where the release of the active compound is controlled by a non-disintegrating membrane.
11. A formulation according to claim 9 where the formulation is an inert porous matrix.
12. A process for the manufacture of a preparation according to claim 11 wherein the active substance is mixed with polymers or materials in an amount exceeding 10% of the weight of the mixture and the resulting mixture is compressed into a tablet.
13. A process according to claim 12 wherein the tablet is heated to a temperature above the melting point of the waxy material to retard the release profile and improve the mechanical strength of the tablet.
14. Use of a formulation according to claim 1 in the preparation of an active dosage form for the treatment of infections in the upper gastrointestinal tract.
15. Use of a formulation according to claim 1 together with acid secretion inhibitors.
16. Use of a formulation according to claim 1 together with proton pump inhibitors.
17. Use according to claim 16 wherein the proton pump inhibitor is omeprazole.

1/1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00521

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/22, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0490450 (BROCADES PHARMA B.V.), 17 June 1992 (17.06.92), see page 2, line 1 - line 47; page 7, line 40 - line 49; example 5; claims 11-15 --	1-6, 14-17
X	WO, A1, 9119486 (KALMO ENTERPRICES, INC.), 26 December 1991 (26.12.91), see page 9, line 4 - page 10, line 17; claims 1-6 --	1-8
X	EP, A2, 0455475 (RECKITT AND COLMAN PRODUCTS LIMITED), 6 November 1991 (06.11.91), see page 2 - page 3, line 47, claims --	1-4, 7-14

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/00521

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Current Opinion in Gastroenterology, Volume 8, 1992, C.S. Goodwin et al, "Peptic ulcer disease and Helicobacter pylori infection" page 122 - page 127 --	1-17
E,A	Dialog Information Services, file 154, MEDLINE, Dilaog accession no. 08302546, MEDLINE accession no. 93012546, Rune S: "Helicobacter pylori, peptic ulcer disease and inhibition of gastric acid sec- retion", Digestion (SWITZERLAND) 1992, 51 Suppl 1 p11-6 -- -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/08/93

International application No.

PCT/SE 93/00521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0490450	17/06/92	AU-A- 9134791 WO-A- 9210502	08/07/92 25/06/92
WO-A1- 9119486	26/12/91	AU-A- 8219191	07/01/92
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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING ANTIULCER AGENT (57) Abstract <p>An enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time is provided, which comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to acid, an undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating. The core portion and/or the undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide-sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer e.g. disodium hydrogenphosphate.</p>		

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DESCRIPTION

PHARMACEUTICAL COMPOSITION CONTAINING ANTIULCER AGENT

[Technical Field]

This invention relates to a pharmaceutical composition containing an antiulcer agent, which composition is improved in stability and unchanged in dissolution property with time.

[Background Art]

2-[(2-Pyridyl)methylsulfinyl] benzimidazole compounds (simply referred to as "benzimidazole compounds") having H^+-K^+ ATPase inhibitory activity are useful as therapeutic agents for digestive ulcers which serve to suppress potently the secretion of gastric acid. The inhibitory activity is so potent and lasting that they have attracted attention as a next-generation therapeutic agent for digestion ulcers which supersedes histamine H_2 receptor antagonists such as cimetidine, etc. In particular, benzimidazole compounds described in Japanese Patent First Publications [41783/1979, 50978/1986 and 6270/1989 have a potent gastric antiulcer activity and are corroborated to have clinical usefulness.

These benzimidazole compounds disclosed, however, have poor stability. That is, they are unstable, in the solid state, to heat, humidity and light, and are susceptible, in an acidic or neutral aqueous solution, to rapid decomposition and significant coloring. Further, in the form of preparations such as tablets, fine granules, granules, capsules and powders, the benzimidazole compounds are adversely affected by other ingredients than them in the preparations and becomes unstable, thus causing decrease in content thereof and color change with

the lapse of time. Of these preparations, where the tablets or granules are applied with an enteric coating, the compatibility of the compounds with the enteric agent (e.g. cellulose acetate/phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, methacrylic acid/acrylic acid copolymer) is so poor that the decrease in content and coloring occur.

The manufacture of oral preparations of benzimidazole compounds necessitates incorporating another ingredients and applying an enteric coating, but the stability of the compounds is thus adversely affected, and consequently, it has been difficult to manufacture the oral preparations.

In the past, in order to obtain a stable pharmaceutical preparation of benzimidazole compounds having antiulcer activity, there has been proposed a method of bringing the compounds into homogeneous contact with a magnesium and/or calcium salt of basic inorganic acid (e.g. heavy magnesium carbonate, magnesium oxide, precipitated calcium carbonate, calcium hydroxide) (Japanese Patent Publication 38247/1991). According to the Publication 38247/1991, the change of the pharmaceutical preparation during storage in appearance and content (residue rate) was measured and as a result, it is reported that there was no change of appearance and the content was stable. However, we, the inventors have traced the Publication according to its method as described by preparing enteric tablets of omeprazole and conducting stability test, and demonstrated that significant coloration and significant decrease in content have been caused because of the effects of

the enteric coating agent and accordingly, sufficiently stable preparations cannot be obtained.

Again, Japanese Patent First Publication 283964/1987 discloses a composition comprising a benzimidazole derivative and its 5% by weight or more of a basic substance (hydroxides or inorganic acid salts of alkali metals, alkali earth metals or aluminum) and its results of preservation stability (residue amount). However, it will be evident that in case where the composition is covered with an enteric coating agent, stable enteric preparations cannot be likewise obtained for the reasons above.

On the other hand, these problems have been solved by a new pharmaceutical preparation which is disclosed in Japanese Patent First Publication 258320/1987. The new preparation is composed of ① a core portion containing an active component, ② an intermediate coating on the core portion consisting of one or more layers and ③ an enteric coating on the intermediate coating, thereby forming a three-coat oral enteric pharmaceutical preparation, wherein the core portion comprises an alkaline reactive compound, e.g. magnesium oxide, magnesium hydroxide, etc. and the intermediate coating comprises a pH buffering alkaline compound, e.g. magnesium oxide, magnesium hydroxide, or complex compound $[\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}]$ or $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ (n is non-integer of less than 2). Thus, the preparation is characterized in that the core portion includes an alkaline reactive compound and the intermediate coating includes a pH buffering alkaline compound. The Applicant of this invention is manufacturing and selling stable

omeprazole preparations wherein magnesium hydroxide is selected as a best alkaline compound and synthetic hydrotalcite, as a pH buffering alkaline compound of the intermediate coating.

However, in the case of the omeprazole preparations in tablet form, problems have occurred in the course of manufacturing process in that since the film formability of the first and second intermediate coating layers is very poor, they cause partial separation and because of brittleness, defective coating films are produced by impact during the manufacturing process, with the result that defective tablets in the intermediate coating coexist. As a consequence, inclusion of reject tablets, which are partially browned because of direct contact of the enteric coating with the core portion, has occurred. Further problem is that the pharmaceutical preparations are unstable to humidity and consequently, when stored under humidifying condition, have caused delay in disintegration of the tablets and impairment of dissolution. Thus the three-coat pharmaceutical preparations are improved in stability; nevertheless, the manufacture of them is likely to produce reject products, and it is a current practice to apply a tight, dampproof package to the tablets for the marketing process, which is not advantageous in economy aspect, as well.

[Disclosure of Invention]

In view of the current situation described above, with a view toward developing more useful preparations of benzimidazole compounds having antiulcer activity and being unstable to acids, a variety of substances have been investigated intensively, and it has been found that the foregoing problems

can be solved by incorporating a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforesaid coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer a mixture of an acid salt of an amino acid and a buffer or a mixture of an alkali salt of an amino acid and a buffer, which has matured to this invention.

This invention is directed to :

(1) an enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound that has antiulcer activity and is unstable to acid, and undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating, wherein said core portion and/or said undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer;

(2) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating

of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide · sodium bicarbonate coprecipitate;

(3) the enteric pharmaceutical composition as set forth in item 2, wherein the aluminum hydroxide · sodium bicarbonate coprecipitate in the undercoating is in the range of 0.01~10 parts by weight based on 100 parts by weight of the core portion;

(4) the enteric pharmaceutical composition as set forth in item 2, wherein the undercoating comprises aluminum hydroxide · sodium bicarbonate coprecipitate and talc;

(5) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer;

(6) the enteric pharmaceutical composition as set forth in item 5, wherein the aluminum hydroxide · sodium bicarbonate coprecipitate and a buffer are in the range of, respectively, 0.01~0.5 part by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound;

(7) the enteric pharmaceutical composition as set forth in item

5, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate;

(8) an enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum glycinate and a buffer;

(9) the enteric pharmaceutical composition as set forth in item 8, wherein the aluminum glycinate and the buffer are in the range of, respectively, 0.1~2 parts by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound;

(10) the enteric pharmaceutical composition as set forth in item 8, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate;

(11) an enteric pharmaceutical composition improved in stability

and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise a mixture of amino acid, an acid salt of an amino acid or an alkali salt of an amino acid and a buffer;

(12) the enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid, or alkali salt of an amino acid is in the range of 0.01~2 parts by weight and the buffer is in the range of 0.01~2 parts by weight, respectively, based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound;

(13) the enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonin, DL-threonin, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparagate, L-lysine or L-lysine-L-glutamate; and the buffer is an alkaline metal salt of phosphoric acid, sodium tartarate, sodium acetate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate;

(14) the enteric pharmaceutical composition as set forth in item

11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, L-alanine, DL-alanine or sodium L-glutamate; and the buffer is disodium hydrogenphosphate.

The 2-[(2-pyridyl)methylsulfinyl] benzimidazole compounds having antiulcer activity and being unstable to acid to be used in this invention are described more specifically in the aforementioned publications. Exemplified are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole), 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl)methyl]-sulfinyl]-1H-benzimidazole (lansoprazole), 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]-methylsulfinyl]-1H-benzimidazole, 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 6-methyl-2-[(3-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole-5-methyl carboxylate, 5-methyl-2-[(3,5-dimethyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 2-[(4-methoxy-2-pyridyl)-methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole, 2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole, 2-[(5-ethyl-4-phenoxy-2-pyridyl)-methylsulfinyl]-5-methoxy-1H-benzimidazole, 5-methoxy-2-[(4-phenoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 2-[(3-methyl-4-(2-(N-benzyl-N-methylamino)ethoxy)-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 2-[(3-methyl-4-(2-morpholinoethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole or 2-[(3-methyl-4-(2-(1,2,3,4-tetrahydroisoquinoline-2-yl)ethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole. The aforementioned compound as an active component is contained in the core

portion in the range of 1 - 50 mg, preferably 5 - 30 mg.

The pharmaceutical preparations as mentioned in 2, 3, 4 above will be described below in more detail:

The amount of the aluminum hydroxide · sodium bicarbonate coprecipitate to be incorporated for the core portion is preferably in the range of 0.01 to 1 part by weight based on 1 part by weight of the benzimidazole compound, but is not limited to this range. The above-mentioned stabilizer may contain further additives used generally in the preparation of pharmaceutical preparations, such as a vehicle, e.g. lactose, mannitol, corn starch, microcrystalline cellulose, a binder, e.g. hydroxypropylcellulose, a disintegrating agent, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename of Explotab by Kimura Sangyo), calcium carboxymethylcellulose, a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), a lubricant, e.g. magnesium stearate, talc, etc.

In accordance with this invention, the core portion can be obtained by admixing homogeneously a benzimidazole compound, aluminum hydroxide · sodium bicarbonate coprecipitate as a stabilizer and, whenever necessary, additives as mentioned above. In admixing, for example, to a mixture of the benzimidazole compound and the stabilizer may be added the additives, or to a mixture of the benzimidazole compound and the additives may be added the stabilizer. The mixture thus obtained is made into powders according to wet granulating method, and then tableted to give core tablets. Alternatively, the mixture is wet kneaded, subsequently granulated with an

extrusion-granulator, and then made into core granules with the aid of Marumerizer (ex Fuji Powdal Co.). This mixing method and method of producing tablets and granules are applicable also to the preparations 5 - 14 which will be described hereinafter.

The pharmaceutical preparations as mentioned in 5, 6, 7 above will be described below:

The amount of the aluminum hydroxide · sodium bicarbonate coprecipitate to be incorporated for the core portion is preferably in the range of 0.01 to 0.5 part by weight based on 1 part by weight of the benzimidazole compound, but is not limited to this range. The above-mentioned stabilizer may contain further additives used generally in the preparation of pharmaceutical preparations, such as a vehicle, e.g. lactose, mannitol, corn starch, microcrystalline cellulose, a binder, e.g. hydroxypropylcellulose, a disintegrating agent, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename of Exprotab by Kimura Sangyo), calcium carboxymethylcellulose, a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), a lubricant, e.g. magnesium stearate, talc, etc. A preferred disintegrating agent is sodium carboxymethylstarch.

In case where the stabilization of the benzimidazole compound is insufficient, depending upon the effects of solution property (pH) of the benzimidazole compound or various additives for pharmaceutical preparations such as vehicle, binder, lubricant, etc., the aluminum hydroxide · sodium bicarbonate coprecipitate can be used in admixture with an water-soluble buffer agent thereby to enhance its stability.

The buffer means a substance added to the coprecipitate to control its pH to 8-9 (weak alkali) and includes, for example, sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, dipotassium hydrogenphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, trisodium phosphate or tripotassium phosphate. The amount of the buffer agent to be added is preferably in the range of 0.01 to 2 parts by weight per 1 part by weight of the benzimidazole compound, but is not limited to this range.

The pharmaceutical preparations as mentioned in 8, 9, 10 above will be described below in more detail:

The buffer to be used in the preparations includes, for example, sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogenphosphate, sodium pyrophosphate, disodium hydrogenphosphate, trisodium phosphate or tripotassium phosphate, among which disodium hydrogenphosphate is preferred.

The amounts of aluminum glycinate and the buffer are preferably in the range of 0.01~2 parts by weight and 0.01~2 parts by weight, respectively, based on 1 part by weight of the benzimidazole compound.

The stabilizer in this invention may be used together with pharmaceutically acceptable additives, for example, an excipient such as lactose, mannitol, cornstarch, crystalline cellulose, etc.; a binder such as hydroxypropylcellulose, etc.; a disintegrator, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename: Explotab by Kimura Sangyo

Co.), calcium carboxymethylcellulose, α -starch, etc.; a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), etc.; a lubricant such as magnesium stearate, talc, etc.

The pharmaceutical preparations as mentioned in 11, 12, 13, 14 above will be described below:

The amino acid, acid salt of an amino acid, or alkali salt of an amino acid in this invention include, for example, glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparaglate, L-lysine or L-lysine-L-glutamate alone or in admixture thereof. Of these compounds, glycine, glycine hydrochloride, L-alanine, DL-alanine or sodium L-glutamate are preferred.

The buffer here means a substance added to the amino acid, etc. to control its pH to 8~9 (weak alkali) and includes, for example, an alkaline metal salt of phosphoric acid (disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium dihydrogenphosphate, potassium dihydrogenophosphate, etc.), sodium tartarate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate. Most preferred is disodium hydrogenphosphate. The amounts of the amino acid or the like and the buffer to be incorporated are preferably in the range of 0.01 ~ 2 parts by weight and 0.01~2 parts by weight, respectively, based on 1 part by weight of the

benzimidazole compound, but are not limited thereto.

The stabilizer in this invention may be used together with pharmaceutically acceptable additives, for example, an excipient such as mannitol, cornstarch, crystalline cellulose, etc.; a binder such as hydroxypropylcellulose, etc.; a disintegrator, e.g. low substituted hydroxypropylcellulose, sodium carboxymethylstarch (tradename: Exprotab by Kimura Sangyo Co.), calcium carboxymethylcellulose, etc.; a surfactant, e.g. sodium laurylsulfate, Tween 80 (tradename), etc.; a lubricant such as magnesium stearate, talc, etc.

Onto the core portion (core tablets, core granules) formed in this manner is covered the undercoating of one or two layers, which may contain aluminum hydroxide · sodium bicarbonate coprecipitate or the coprecipitate and buffer, aluminum glycinate and buffer, etc. as a stabilizer. The undercoating agent includes polymers, preferably, pharmaceutically acceptable water-soluble polymers selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, gelatine, etc., or saccharides such as purified sucrose, mannitol, lactose, etc. Further, additives such as talc, titanium oxide, light silicic acid anhydride may be added.

The undercoating is preferably composed of two layers. The one undercoating layer on the core portion side comprises aluminum hydroxide · sodium bicarbonate coprecipitate, a polymer or saccharide and additives such as talc, whereas the other undercoating layer on the enteric coating side comprises a polymer or saccharide and, whenever necessary, additives such

as talc. The amount of the stabilizer to be incorporated in the undercoating is preferably in the range of 0.01 to 10 parts by weight based on 100 parts by weight of the core portion, but is not limited to the range.

The intermediate product thus obtained can be covered with an enteric coating to give an enteric pharmaceutical preparation. As the enteric coating there may be mentioned cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, methacrylic acid/acrylic acid copolymer (tradename : Eudragit), etc., and a plasticizer and a pigment may also be incorporated.

As described above, in the 3-coat pharmaceutical preparation comprising the core portion, undercoating and enteric coating, it is essential to incorporate a stabilizer, namely aluminum hydroxide · sodium bicarbonate coprecipitate, etc. for the core portion and/or the undercoating. If any of the requisites is lacking, the intended preparation cannot be obtained. In the pharmaceutical preparations according to Japanese Patent First Publication 258320/1987, if magnesium hydroxide added to the core portion is incorporated also in the undercoating, the enteric coating will be affected adversely thereby. In order to avoid it, in a best preparation of them, a synthetic hydrotalcite is therefore used for the undercoating.

In contrast, according to this invention, a stabilizer such as aluminum hydroxide · sodium bicarbonate coprecipitate added to the core portion is also incorporated in the undercoating. Thereby, the film formability of the undercoating agent (e.g. hydroxypropylmethylcellulose) is good as compared with that of

the undercoating containing synthetic talc. By the incorporation of a stabilizer such as aluminum hydroxide · sodium bicarbonate coprecipitate and talc in the undercoating, slip of the undercoating during its manufacture is improved and impact during the manufacture is minimized, whereby the occurrence of deficiency of the film is impeded and no rejects of browned tablets are produced accordingly.

It is thus possible to obtain dosage forms suitable for oral administration, namely enteric tablets, granules and capsules encapsulating therein granules. The pharmaceutical preparations in the dosage forms thus obtained have the following characteristics:

- (1) Even if they are stored under severe conditions for a long period of time, there are seen no impairment in appearance and little decrease in content.
- (2) Under humidification at high temperature, the disintegration property is good and dissolution property is not impaired.
- (3) The film formability of the undercoating is superior. Consequently, reject products in the manufacturing process are decreased, leading to curtailment of cost.
- (4) It is possible to simplify the package of products. A longer stability after seal-opening in pharmacys or else can be ensured.

The pharmaceutical preparations of this invention have good gastric antisecretory activity and antiulcer activity, so that they can be used for the treatment of ulcers of digestive organs, etc. in mammals inclusive of the human.

[Brief Description of Drawings]

Fig. 1 is a graphical representation showing the profile of dissolution of omeprazole tablets obtained in Reference Example 1-1;

Fig. 2 is a graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 1-2;

Fig. 3 is another graphical representation showing the profile of dissolution of omeprazole tablets obtained in Reference Example 1-1;

Fig. 4 is another graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 1-2;

Fig. 5 is a graphical representation showing appearance change of Samples 4, 5, 6 and 7 in Experimental Example 1-4, when preserved, in terms of ΔE value.

Fig. 6 is a graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 2-2;

Fig. 7 is another graphical representation showing the profile of dissolution of omeprazole tablets of this invention obtained in Example 2-2;

[Best Mode for Carrying out the Invention]

The invention will be hereinbelow described in more detail by way of reference examples, examples and experimental examples, but should not be construed as limiting to them.

Reference Example 1-1

Enteric tablets were produced by using magnesium hydroxide as a stabilizer for the core portion and synthetic hydrotalcite

as a stabilizer for the undercoating in accordance with the method of Japanese Patent First Publication 258320/1987 as follows:

Tablets (135 mg) containing 20 mg of omeprazole and magnesium hydroxide were formed by means of a rotary tableting machine. The core tablets thus obtained were applied with an undercoating of hydroxypropylmethyl cellulose containing 0.3 mg of synthetic talcite to form a first undercoating layer and further applied with an undercoating solution of hydroxypropylmethyl cellulose to form a second undercoating layer. Then an enteric coating solution containing hydroxypropylmethyl cellulose phthalate was applied onto the second undercoating layer to give enteric tablets.

Example 1-1

The composition given below was placed into a kneader to mix it for about 20 minutes and kneaded with an adequate amount of purified water. The mixture was extruded, granulated with a granulating machine (screen diameter of 1.0 mm) and made into spherical granules with Marumerizer (ex Fuji Powdal). The granules were dried in a fluidized bed drier at an air supply temperature of 50 °C for 30 minutes and passed through a sieve to give core granules of 14 to 24 meshes.

Omeprazole	5.0 mg
Aluminum hydroxide · sodium bicarbonate coprecipitate	5.0 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.5 mg

Total	75.0 mg
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The core granules were applied with coatings given below to give enteric granules. The first and second undercoatings were applied in a fluidized spray drier (manufactured by Ohkawara Co.) at an air supply temperature of 75°C and an exhaust temperature of 45°C whereas the enteric coating was applied at an air supply temperature of 65°C and an exhaust temperature of 40°C.

Core granules	75.0 mg
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Undercoating 1

Hydroxypropylmethylcellulose	3.5 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)

Total	13.0 mg
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Example 1-2

Omeprazole, aluminum hydroxide • sodium bicarbonate coprecipitate, lactose, sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylmethyl cellulose in respective amounts given below were mixed homogeneously, kneaded with an adequate amount of purified water and dried in a fluidized bed drier at an air supply temperature of 50°C for 30 minutes. After granulating, the granules were passed through a screen of 24 meshes and mixed with magnesium stearate. The mixture was tableted with a rotary tableting machine to give tablets (core tablets) each of 135 mg.

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	15.0 mg
Lactose	91.2 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.5 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

To the core tablets are applied coatings as given below to give enteric tablets. The first and second undercoatings were applied with Highcoater (by Freund Sangyo) at an air supply temperature of 70°C and an exhaust temperature of 40°C at a pan revolution number of 15 rpm. The enteric coating was applied at an air supply temperature of 55°C and an exhaust temperature of 37°C.

Core tablets	135.0 mg
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Undercoating 1

Hydroxypropylmethylcellulose	1.2 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.3 mg
Talc	0.1 mg
Purified water	(23.0 mg)
Total	1.6 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Talc	0.1 mg
Purified water	(56.0 mg)
Total	4.2 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.9 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.2 mg
Aggregate	144.0 mg

Experimental Example 1-1

With the enteric tablets obtained in Reference Example 1-1 and Example 1-2 of this invention, preparation characteristics and preservation stability were examined and yielded the results that there were seen no differences between the both as shown in Tables 1-1 and 1-2.

Table 1-1 Preparation Characteristics

	Reference Example 1-1	Example 1-2
Weight (mg)	143.0	144.0
Diameter (mm)	7.13	7.13
Thickness (mm)	3.23	3.24
Hardness (kp)	13.0	14.0
Disintegration (The Pharmacopeia of Japan, 12 Ed.)		
The 1st fluid		
(Durability after 2 hr.)	Compliance	Compliance
The 2nd fluid	4.7 min	5.8 min
Dissolution (the 2nd fluid, paddle method, 100 rpm)		
10 min.	89.3%	96%
20 min.	100.4%	100.3%
Stability against of the 1st fluid (the 1st fluid, paddle method, 100 rpm)		
Residue rate of active		
ingredient after 2 hr.	99.8%	99.8%

Table 1-2 Stability

Preservation Conditions	Reference Example 1-1		Example 1-2	
	Appearance	Content(%)	Appearance	Content(%)
Initial	white	99.7	white	99.7
40°C, one month	white	99.3	white	99.6
40°C, two months	white	100.0	white	99.5
60°C, two weeks	white	99.3	white	99.5
60°C, one month	white	99.5	white	99.2
40°C, 75%RH, two weeks	white	99.3	white	99.5
40°C, 75%RH, one month	white	99.3	white	99.3

Experimental Example 1-2

Enteric tablets of omeprazole obtained in Reference Example 1-1 and Example 1-2 were preserved for two weeks under conditions of 25°C, 85% relative humidity and 40°C, 82% relative humidity and thereafter, dissolution test was carried out to determine dissolution rate in the 2nd fluid (pH : ca. 6.8) according to The Japan Pharmacopoeia. The results obtained are shown in Fig.1 to Fig.4.

As will be apparent from Fig.1 and Fig.3, significant deterioration in dissolution was observed with the enteric tablets in Reference Example 1-1 under reservation at 25°C, 85% RH (Fig.1) and at 40°C, 82% RH (Fig.3). On the other hand, it is evident from Fig.2 and Fig.4 that no reduction in dissolution was observed with the enteric tablets of Example 1-2 even after storage of two weeks at 25°C, 85% RH (Fig.2) and at 40°C, 82% RH (Fig.4)

Example 1-3

Enteric tablets of omeprazole comprising the following compositions are produced according to the method of Example 1-2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide · sodium bicarbonate coprecipitate	0.5 mg
Lactose	101.0 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.2 mg
Hydroxypropylmethylcellulose	0.3 mg
Magnesium stearate	0.5 mg

Total	130.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.1 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.4 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.0 mg
Titanium oxide	0.5 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.6 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.7 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.0 mg
Aggregate	138.0 mg

Example 1-4

Enteric tablets of omeprazole comprising the compositions given below are produced according to the method of Example 1-2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium	

bicarbonate coprecipitate	1.0 mg
Lactose	100.5 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.2 mg
Hydroxypropylmethylcellulose	0.3 mg
Magnesium stearate	0.5 mg
Total	130.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.3 mg
Talc	0.2 mg
Purified water	(20.0 mg)
Total	1.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.9 mg
Titanium oxide	0.5 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.7 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.0 mg
Aggregate	138.0 mg

Example 1-5

Enteric preparation having the compositions given below is produced according to the method of Example 1-2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	2.5 mg
Lactose	103.8 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.4 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.2 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.3 mg
Talc	0.1 mg
Purified water	(23.0 mg)
Total	1.6 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	4.2 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.9 mg
Cetanol	0.1 mg
Talc	0.2 mg

Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.2 mg
Aggregate	144.0 mg

Example 1-6

Enteric preparation of omeprazole having the compositions given below is produced according to the method of Example 2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	2.5 mg
Lactose	103.7 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.5 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.2 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.3 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.6 mg

Undercoating 2

Hydroxypropylmethylcellulose	4.65mg
Titanium oxide	1.5 mg
Talc	0.15mg
Purified water	(45.0 mg)

Total	6.3 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.9 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.2 mg
Aggregate	146.1 mg

Example 1-7

Enteric preparation of omeprazole having the compositions given below is produced according to the method of Example 1-2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	5.0 mg
Lactose	101.3 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.4 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.6 mg
Talc	0.2 mg
Purified water	(20.0 mg)
Total	1.8 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.0 mg
Titanium oxide	1.5 mg
Talc	0.2 mg
Purified water	(45.0 mg)
Total	4.7 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	3.0 mg
Cetanol	0.2 mg
Talc	0.3 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.5 mg
Aggregate	145.0 mg

With the preparations of Examples 1-3 to 1-7, there was observed little change in appearance with the lapse of time.

Experimental Example 1-3

Enteric preparation of omeprazole having the compositions below is produced according to the method of Example 1-2.

(Sample 1)

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	2.5 mg
Lactose	103.8 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.4 mg
Magnesium stearate	0.5 mg

Total	135.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.3 mg
Talc	0.2 mg
Purified water	(20.0 mg)
Total	1.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.9 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.0 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.7 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.0 mg
Aggregate	142.5 mg

Enteric preparation of omeprazole having the compositions
given below is produced according to the method of Example 1-2.

(Sample 2)

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	2.5 mg
Lactose	103.8 mg

Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.4 mg
Magnesium stearate	0.5 mg
Total	135.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide • sodium bicarbonate coprecipitate	0.6 mg
Talc	0.2 mg
Purified water	(20.0 mg)
Total	1.8 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.6 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.7 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.7 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.0 mg
Aggregate	142.5 mg

Enteric preparation of omeprazole having the compositions
given below is produced according to the method of Example 1-2.

(Sample 3)

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	2.5 mg
Lactose	103.8 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	0.4 mg
Magnesium stearate	0.5 mg
Total	135.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.0 mg
Synthetic hydrotalcite	0.3 mg
Talc	0.2 mg
Purified water	(20.0 mg)
Total	1.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.9 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.0 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.7 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(3.0 mg)
Purified water	(8.5 mg)
Total	3.0 mg
	142.5 mg

The preparations of Sample 1 to Sample 3 were preserved for

2 weeks and 1 month under the conditions of 40°C, 82% RH, and thereafter, change in appearance of them was measured with a colorimeter to determine ΔE values of them. The results obtained are shown in Table 1-3.

Table 1-3

Preparation	40°C, 82% RH	
	ΔE after 2 weeks	ΔE after 1 month
Sample 1	2.3	5.5
Sample 2	2.4	5.9
Sample 3	3.9	7.7

The preparations (Samples 1, 2) incorporating aluminum hydroxide-sodium bicarbonate coprecipitate in Undercoating 1 were more stable than the preparation (Sample 3) incorporating synthetic talcite in Undercoating 1.

Reference Example 1-2

Enteric tablets of lansoprazole of the following composition are produced according to the method of Reference Example 1-1.

Core tablets

Lansoprazole	20.0 mg
Magnesium hydroxide	10.0 mg
Lactose	73.5 mg
Sodium carboxymethylstarch	5.0 mg
Sodium laurylsulfate	0.2 mg
Hydroxypropylcellulose	0.8 mg
Magnesium stearate	0.5 mg
Total	110.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Synthetic hydrotalcite	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.3 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.6 mg
Titanium oxide	0.8 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg
Talc	0.1 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	117.5 mg

Reference Example 1-3

Enteric tablets of 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazol (designated as Compound 1) comprising the following compositions are produced according to the method of Reference Example 1-1.

Core tablets

Compound 1	20.0 mg
Magnesium hydroxide	20.0 mg
Lactose	31.0 mg

Low substituted hydroxypropylcellulose	8.0 mg
Hydroxypropylmethylcellulose	0.7 mg
Magnesium stearate	0.3 mg
Total	80.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	0.8 mg
Synthetic hydrotalcite	0.15mg
Talc	0.05mg
Purified water	(20.0 mg)
Total	1.0 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.4 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.5 mg
Enteric coating	
Hydroxypropylmethylcellulose	2.0 mg
Cetanol	0.8 mg
Talc	0.7 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.5 mg
Aggregate	87.0 mg

Enteric tablets are produced similarly by using 2-[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole (designated as Compound 2) instead of Compound 1.

Example 1-8.

Enteric tablets of lansoprazole having the compositions

below are produced according to the method of Example 1-2.

Core portion

Lansoprazole	20.0 mg
Aluminum hydroxide·sodium bicarbonate coprecipitate	10.0 mg
Lactose	73.5 mg
Sodium carboxymethylstarch	5.0 mg
Sodium laurylsulfate	0.2 mg
Hydroxypropylmethylcellulose	0.8 mg
Magnesium stearate	0.5 mg
Total	110.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide·sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.3 mg

Undercoating 2

Hydroxypropylmethylcellulose	2.6 mg
Titanium oxide	0.8 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	3.5 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg
Talc	0.1 mg
Ethanol	(30.0 mg)

Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	117.5 mg

Experimental Example 1-4

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 4)

Core tablets

Lansoprazole	20.0 mg
Lactose	106.0 mg
Sodium carboxymethylstarch	7.5 mg
Hydroxypropylmethylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.3 mg

Undercoating 2

Hydroxypropylmethylcellulose	2.6 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.7 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg

Talc	0.1 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	141.7 mg

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 5)

Core tablets

Lansoprazole	20.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	1.0 mg
Lactose	105.0 mg
Sodium carboxymethylstarch	7.5 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.3 mg

Undercoating 2

Hydroxypropylmethylcellulose	2.6 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.7 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg
Talc	0.1 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	141.7 mg

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 6)

Core tablets

Lansoprazole	20.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	5.0 mg
Lactose	101.0 mg
Sodium carboxymethylstarch	7.5 mg
Hydroxypropylmethylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)
Total	1.3 mg

Undercoating 2

Hydroxypropylmethylcellulose	2.6 mg
------------------------------	--------

Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.7 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg
Talc	0.1 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	141.7 mg

Enteric preparation of lansoprazole having the compositions given below is produced according to the method of Example 1-2.

(Sample 7)

Core tablets

Lansoprazole	20.0 mg
Aluminum hydroxide·sodium bicarbonate coprecipitate	15.0 mg
Lactose	91.0 mg
Sodium carboxymethylstarch	7.5 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	1.0 mg
Aluminum hydroxide·sodium bicarbonate coprecipitate	0.2 mg
Talc	0.1 mg
Purified water	(20.0 mg)

Total	1.3 mg
Undercoating 2	
Hydroxypropylmethylcellulose	2.6 mg
Talc	0.1 mg
Purified water	(45.0 mg)
Total	2.7 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.5 mg
Cetanol	0.1 mg
Talc	0.1 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	2.7 mg
Aggregate	141.7 mg

The preparations of Samples 4 to 7 were preserved for 2 and 4 weeks under the conditions of 40°C, 75% RH and thereafter, change in appearance of them was measured with a colorimeter to determine ΔE values of them. The results obtained are given in Table 1-4 and Fig. 5.

Table 1-4

Preparation	40°C, 75% RH	
	ΔE	
	after 2 weeks	after 4 weeks
Sample 4	5.1	6.6
Sample 5	2.6	3.7
Sample 6	3.1	4.0
Sample 7	2.7	3.6

It was proved that the preparations of Samples 5, 6, 7 incorporating aluminum hydroxide-sodium bicarbonate coprecipitate in core tablets have a smaller ΔE value and lower appearance change as compared with the preparation of Sample 4 not incorporating the coprecipitate.

Example 1-9

Enteric tablets of 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole (Compound 1) are produced according to the method of Example 2.

Core tablets

Compound 1	20.0 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	20.0 mg
Lactose	31.0 mg
Low substituted Hydroxypropylcellulose	8.0 mg
Hydroxypropylmethylcellulose	0.7 mg
Magnesium stearate	0.3 mg
Total	80.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	0.8 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	0.15mg
Talc	0.05mg
Purified water	(20.0 mg)
Total	1.0 mg

Undercoating 2

Hydroxypropylmethylcellulose	2.4 mg
Talc	0.1 mg
Purified water	(45.0 mg)

Total	2.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	2.0 mg
Cetanol	0.8 mg
Talc	0.7 mg
Ethanol	(30.0 mg)
Purified water	(8.5 mg)
Total	3.5 mg
Aggregate	87.0 mg

Enteric tablets of 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole (Compound 2) are similarly produced except that Compound 2 is used instead of Compound 1.

Experimental Example 1-5

Similar tests to Experimental Examples 1-1, 1-2 are performed with the enteric tablets obtained in Reference Example 1-2 and Example 1-8 and the enteric tablets of Compound 1 and Compound 2 obtained in Reference Example 1-3 and Example 1-9, and as a result, a good preservation stability and an improved dissolution characteristic are attained with all the tablets.

Example 1-10

Core tablets of omeprazole having the following composition were produced by wet granulating method according to Example 1-2 by the use of aluminum hydroxide·sodium bicarbonate coprecipitate as a stabilizer.

Core tablets

Omeprazole	20.0 mg
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Aluminum hydroxide-sodium bicarbonate coprecipitate	10.0 mg
Lactose	95.7 mg
Sodium carboxymethylstarch	7.5 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylmethylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Onto the core tablets, Undercoating 1, Undercoating 2 and Enteric coating having the compositions given below were applied according to Example 1-2.

Undercoating 1

Hydroxypropylmethylcellulose	1.2 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	0.3 mg
Talc	0.1 mg
Purified water	(23.0 mg)
Total	1.6 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Talc	0.1 mg
Purified water	(56.0 mg)
Total	4.2 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	2.9 mg
Cetanol	0.1 mg
Talc	0.2 mg
Ethanol	(35.0 mg)

Purified water	(10.0 mg)
Total	3.2 mg
Aggregate	144.0 mg

On the other hand, core tablets were similarly produced by wet granulating method except that magnesium hydroxide, magnesium oxide or calcium hydroxide was used instead of aluminum hydroxide·sodium bicarbonate coprecipitate, and then similarly applied with film coatings to give enteric tablets.

The enteric tablets thus obtained were preserved for 1 week at 50°C, 75% RH or for 2 weeks at 40°C, 75% RH and thereafter, determined of disintegration time according to the test of the Pharmacopoeia of Japan with the 2nd fluid without using the auxiliary disk. The results obtained are shown in Table 1-5.

Table 1-5

Stabilizer		Disintegration Time (min.)		
		Initial value	50°C, 75% RH, 1 Week	40°C, 75% RH, 2 Weeks
This Invention	Aluminum hydroxide·sodium bicarbonate coprecipitate	4.0	3.5	3.9
Control	Magnesium hydroxide	3.0	29.0	7.5
do.	Magnesium oxide	25.0	>30	>30
do.	Calcium hydroxide	20.0	22.0	>30

The enteric tablets of this invention using aluminum hydroxide·sodium bicarbonate coprecipitate exhibited good disintegration property immediately after preparation (at initial stage) and during preservation in a high temperature, humidified condition. In contrast, those of magnesium hydroxide were deteriorated significantly under humidification

at high temperature. The enteric tablets using magnesium oxide and calcium hydroxide, respectively, were poor in disintegration property from the initial stage thereof as prepared.

Example 2-1

The composition given below was placed in a kneader and mixed for about 20 minutes, and kneaded together by adding an appropriate amount of purified water. After granulation with an extrusion-granulator (screen diameter: 1.0 mm), the granules were made into spherical granules with Marumerizer (manufactured by Fuji Powder). The granules were dried in a fluidized drier at 50 °C for 30 min. and passed through a sieve of 14 to 24 meshes to give core granules.

Omeprazole	5.0 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	5.0 mg
Trisodium phosphate ($\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$)	0.5 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.0 mg
Total	75.0 mg

The coatings given below were applied onto the core granules thus obtained to give enteric granules. Undercoating 1 and Undercoating 2 were applied in a fluidized spray drier (manufactured by Ohkawara) at an air supply temperature of 75°C and an exhaust temperature of 45°C; and the enteric coating was applied at an air supply temperature of 65°C and an exhaust temperature of 40°C.

Core granules	75.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	3.5 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg

Reference example 2-1

Core granules were produced in a similar procedure to Example 2-1 except that mannitol was used instead of aluminum hydroxide•sodium bicarbonate coprecipitate and trisodium phosphate. Then, coatings similar to Example 2-1 except that talc was additionally incorporated instead of the aluminum hydroxide•sodium bicarbonate coprecipitate in Undercoating 1

were applied to yield enteric granules of omeprazole.

Experimental Example 2-1

The enteric granules of omeprazole obtained in Example 2-1 and Reference Example 2-1 were placed in a glass bottle and preserved sealingly at 60°C or under open condition of 75% RH at 40°C for 2 weeks. The change in appearance is shown in Table 2-1.

Table 2-1

	At the start	60°C sealed	40°C, 75% RH open
Example 6	white	white	white
Ref. Example 4	pale brown	brown	brown

As will be apparent from Table 2-1, the enteric granules, which contain aluminum hydroxide·sodium bicarbonate coprecipitate and the buffer agent in the core granules aluminum hydroxide·sodium bicarbonate coprecipitate in the undercoating layer, showed no change in appearance even under severe conditions.

Example 2-2

Of the composition given below, aluminum hydroxide·sodium bicarbonate coprecipitate, lactose, sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylcellulose were mixed homogeneously, and an appropriate amount of purified water dissolving therein sodium pyrophosphate was added. The mixture was kneaded and dried in a fluidized bed drier at 50°C for 30 minutes. The dried powders were passed through a sieve of 24 meshes, and magnesium stearate was further added thereto and mixed. Then, the mixture was made into tablets (core tablets)

each of 135 mg with a rotary tableting machine.

Omeprazole	20.0 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	20.0 mg
Sodium pyrophosphate	2.0 mg
Lactose	83.2 mg
Sodium carboxymethylstarch	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The coatings given below were applied to the core tablets thus obtained to give enteric tablets. Undercoatings 1, 2 were applied with Highcoater (Freund Sangyo) at an air supply temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. The enteric coating was applied at an air supply temperature of 55°C and an exhaust temperature of 37°C.

Core tablets	135.0 mg
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Undercoating 1

Hydroxypropylmethylcellulose	1.4 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	0.4 mg
Talc	0.1 mg
Purified water	(23.0 mg)
Total	1.9 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg

Purified water	(56.0 mg)
Total	4.1 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg
Aggregate	144.5 mg

With the enteric tablets of omeprazole thus obtained, dissolution rate in the 2nd fluid (pH: ca. 6.8) according to the Pharmacopoeia of Japan was determined after reservation under conditions of 25°C, 85% RH and 40°C, 82% RH respectively for 2 weeks. The results are shown in Fig. 6 and Fig. 7. As will be apparent from Figs. 6,7, the enteric tablets of this invention using aluminum hydroxide-sodium bicarbonate coprecipitate and the buffer agent (sodium pyrophosphate) exhibited persistently a good dissolution property after preservation under a humidified condition at a high temperature as well as immediately after preparation.

Example 2-3

Enteric tablets of omeprazole of the composition given below are produced according to the method of Example 2-2.

Core tablets

Omeprazole	20.0 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	13.0 mg
Sodium pyrophosphate	2.0 mg

Lactose	83.0 mg
Sodium carboxymethylstarch	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.4 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	0.4 mg
Talc	0.1 mg
Purified water	(23.0 mg)
Total	1.9 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg
Aggregate	144.0 mg

Stability test and dissolution test were performed with the enteric tablets of omeprazole thus obtained, under preservation, and as a result, a good preservation stability and

a high dissolution rate were attained.

Experimental Example 3-1

A quantity of 100 mg of omeprazole, aluminum glycinate and disodium hydrogenphosphate as a buffer were dispersed in 20 ml of water and preserved at 25°C. The resulting white suspension was observed of the appearance change with the lapse of day.

Control solutions containing no aluminum glycinate and no buffer, respectively were also prepared and observed of the change in appearance at 25°C with the lapse of day.

Table 3-1

	Substance added		mg	Change in appearance at 25°C		
				1 day	3 day	7 day
THE IN- VEN- TION	Aluminum glycinate		100			
	$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$		30	white	white	white
	Aluminum glycinate		100			
	$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$		100	white	white	white
	None		-	pale violet	violet	blackish violet
CON- TROL	Ant- acid	Aluminum glycinate	200	slightly violet	brown	brown
		Aluminum hydroxide	200	violet	violet	violet
		Magnesium carbonate	200	white	Slightly brown	pale brown
		Synthetic hydrotalcite	200	white	Slightly gray	pale brown
	Bu- ffer	$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	200	pale brown	pale brown	pale brown
		Sodium tartarate	200	pale violet	violet	violet
		Sodium acetate	200	slightly brown	pale violet	pale violet
		Sodium bicarbonatete	200	white	slightly brown	pale violet
		Sodium polyphosphate	200	slightly brown	slightly brown	pale brown
		Dipotassium hydrogenphospahte	200	pale brown	pale brown	pale brown

From the results above, it is apparent that the conjoint use of aluminum glycinate and a buffer does not discolor omeprazole as compared with single use of aluminum glycinate or

a buffer alone, and accordingly, stabilizes omeprazole.

Example 3-1

The composition mentioned below was charged into a kneader for mixing for about 20 minutes, kneaded by adding an appropriate amount of purified water, granulated on an extrusion granulator (screen diameter of 1.0 mm), and made into spherical granules with the aid of Marumerizer (Fuji Powder Co.). The granules thus obtained were dried in a fluidized bed drier at an air feed temperature of 50 °C for 30 minutes and filtered through a sieve to give granules of 14~24 meshes.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	54.5 mg
Total	75.0 mg

Example 3-2

The composition given below was made into granules according to Example 3-1. Of the composition, disodium hydrogenphosphate was incorporated by dissolving it in purified water.

Omeprazole	5.0 mg
Aluminum glycinate	5.0 mg
Na ₂ HPO ₄ · 12H ₂ O	1.5 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg

Hydroxypropylcellulose	0.5 mg
Mannitol	55.0 mg
Total	75.0 mg

Example 3-3

The granules obtained in Example 3-2 were applied with the coatings given below to give enteric granules. Undercoatings 1 and 2 were applied in a fluidized spray drier (Okawara Co.) at an air feed temperature of 75°C and an exhaust temperature of 55°C whereas Enteric coating was applied in the same drier at an air feed temperature of 65°C and an exhaust temperature of 50°C.

The granules in Example 3-2 75.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	3.5 mg
Aluminum glycinate	1.4 mg
Na ₂ HPO ₄ ·12H ₂ O	0.1 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg

Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg

The enteric granules of omeprazole thus obtained had a good dissolution property and were stable after preservation under heating or humidifying conditions.

Example 3-4

Of the composition given below, omeprazole, aluminum glycinate, mannitol, α -starch, sodium laurylsulfate and hydroxypropylcellulose were homogeneously mixed, and to the mixture, an appropriate amount of purified water dissolving therein sodium pyrophosphate was added to carry out kneading, followed by drying in a fluidized drier at 50°C for 30 minutes.

The dried granules thus obtained were passed through a sieve of 24 mesh and added and mingled with magnesium stearate. Then the granules were made into tablets (core) of 135 mg per one tablet by means of a rotary tableting machine.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Sodium pyrophosphate	1.0 mg
Mannitol	71.7 mg
α -Starch	20.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	1.0 mg
Total	135.0 mg

Example 3-5

The tablets (core) obtained in Example 3-4 were applied with coatings of the compositions given below to give enteric tablets. Undercoatings 1 and 2 were applied with High-coater (Freund Sangyo Co.) at an air feed temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. Enteric coating was applied with the same device at an air feed temperature of 55°C and an exhaust temperature of 37°C.

Tablets of Example 3-4	135.0 mg
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Undercoating 1

Hydroxypropylcellulose	1.5 mg
Aluminum glycinate	0.35mg
Na ₂ HPO ₄ · 12H ₂ O	0.05mg
Purified water	(23.0 mg)
Total	1.9 mg

Undercoating 2

Hydroxypropylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg

Aggregate

144.5 mg

Example 3-6

Core granules of the composition given below were produced according to Example 3-1. The sodium pyrophosphate used was incorporated by dissolving it in purified water. In order to prevent an adverse effect of proton released from the enteric film upon omeprazole, aluminum glycinate and $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ were incorporated in Undercoating 1. Coating was conducted by the use of a fluidized bed drier (Okawara Co.). Undercoatings 1 and 2 were applied at an air feed temperature of 75°C, an exhaust temperature of 55°C and Enteric coating was likewise applied at an air feed temperature of 55°C and an exhaust temperature of 40°C.

Core granules

Omeprazole	5.0 mg
Aluminum glycinate	10.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	44.5 mg
Total	70.0 mg

Undercoating 1

Hydroxypropylcellulose	3.2 mg
Aluminum glycinate	1.2 mg
$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)

Total	5.0 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg
Purified water	(65.0 mg)
Total	5.0 mg
Enteric coating	
Methacrylic acid/acrylic acid copolymer	
(solid content)	15.0 mg
Polyethylene glycol 6000	1.3 mg
Tween 80	0.7 mg
Talc	3.0 mg
Purified water	(50.0 mg)
Total	20.0 mg

Reference Example 3-1

Tablets (core tablets) were produced from the composition given below according to Example 3-4.

Omeprazole	20.0 mg
Mannitol	13.2 mg
α -Starch	20.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

To the tablets (core tablets) obtained were applied Undercoating 2 and Enteric coating applied in Example 3-5 to give enteric tablets.

Reference Example 3-2

The composition of the formulation given below was made into tablets (core tablets) according to Example 3-4.

Omeprazole	20.0 mg
Aluminum glycinate	20.0 mg
Mannitol	73.2 mg
α -Starch	21.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

The tablets (core tablets) thus obtained were applied with the film coatings in Example 3-5 to yield enteric tablets.

Experimental Example 3-2

The core tablets obtained in Example 3-4, the enteric tablets in Example 3-5, the core tablets and enteric tablets in Reference Example 3-1 and the core tablets and enteric tablets in Reference Example 3-2 were respectively placed in a glass bottle, and allowed to stand for 2 weeks with the bottles sealingly stoppered under 60°C condition and opened under 40 °C, 75% RH conditions, respectively. The results obtained of the change in appearance are shown in Table 3-2.

Table 3-2

	As prepared	Sealingly stoppered at 60°C	Opened at 40°C 75% RH
Example 3-4 (core tablets)	white	white	white
Example 3-5 (enteric tablets)	white	white	white
Ref. Example 3-1 (core tablets)	slightly brown	pale brown	pale brown
ditto (enteric tablets)	white	slightly brown	pale brown
Ref. Example 3-2 (core tablets)	pale brown	pale brown	pale brown
ditto (enteric tablets)	slightly brown	pale brown	pale brown

As will be apparent from the results in Table 3-2, the change in appearance was significantly improved by incorporating aluminum glycinate and a buffer.

Experimental Example 3-3

Tablets (core tablets) were produced in the formulation given below according to Example 3-4 (Sample A).

Omeprazole	20.0 mg
Aluminum glycinate	10.0 mg
sodium pyrophosphate	10.0 mg
Na ₂ HPO ₄ · 12H ₂ O	2.0 mg
Mannitol	87.5 mg
Carboxymethylcellulose	10.0 mg
Magnesium stearate	0.5 mg
Total	130.0 mg

Tablets (core tablets) containing no stabilizer were produced in the formulation given below according to Example 3-4 (Control A).

Omeprazole	20.0 mg
Mannitol	99.5 mg
Carboxymethylcellulose	10.0 mg
Magnesium stearate	0.5 mg
Total	130.0 mg

Sample A and Control A were preserved under 40°C, 75% RH conditions for 4 weeks and then measured of change in appearance with a colorimeter to determine ΔE values. The results obtained are shown below.

Preparation	ΔE
Sample A	7.0
Control A	14.0

As will be apparent from the experimental results, in case where aluminun glycinate or a buffer alone is incorporated in omeprazole no stabilization effect was attained whereas the conjoint use of both can stabilize significantly omeprazole, and accordingly, a stabilized preparation containing antiulcer agent was obtained.

Experimental Example 4-1

A quantity of 100 mg of omeprazole, 100 mg of various amino acid and 100 mg of disodium hydrogenphosphate as a buffer were dispersed in 20 ml of water and preserved at 25°C. The resulting white suspension was observed of the appearance change with the lapse of day.

Control solutions containing no amino acid and no buffer, respectively were also prepared and observed of the change in appearance at 25°C with the lapse of day.

Table 3-1

	Substance added		mg	Change in appearance at 25°C		
				1 day	3 days	7 days
THE IN- VEN- TION	Glycine		100			
	Na ₂ HPO ₄ • 12H ₂ O		100	white	white	white
	L-Isoleucine		100			
	Na ₂ HPO ₄ • 12H ₂ O		100	white	white	white
	L-Alanine		100	white	white	gray
	Na ₂ HPO ₄ • 12H ₂ O		100			
	L-Threonine		100	white	white	gray
	Na ₂ HPO ₄ • 12H ₂ O		100			
	L-Phenylalanine		100	white	white	gray
	Na ₂ HPO ₄ • 12H ₂ O		100			
CON- TROL	None		-	pale violet	violet	blackish violet
	Amino acid	Glycine	100	violet	violet	blackish violet
		L-Alanine	100	pale violet	violet	blackish violet
		L-Isoleucine	100	slightly brown	violet	blackish violet
	Bu- ffer	Na ₂ HPO ₄ • 12H ₂ O	200	pale brown	pale brown	pale brown
		Sodium tartarate	200	pale violet	violet	violet
		Sodium pyrophosphate	200	slightly brown	slightly brown	pale brown
		Sodium acetate	200	slightly brown	pale violet	pale violet
		Sodium bicarbonate	200	white	slightly brown	pale violet

	Sodium polyphosphate	200	slightly brown	slightly brown	pale brown
	Dipotassium hydrogenphosphate	200	pale brown	pale brown	pale brown
	Magnesium carbonate	200	white	slightly brown	pale brown

From the results above, it is apparent that the conjoint use of an amino acid and a buffer does not discolor omeprazole as compared with single use of an amino acid or a buffer alone, and accordingly, stabilizes omeprazole.

Example 4-1

Of the composition given below, omeprazole, crystalline cellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose and mannitol were charged into a kneader and mixed for ca. 20 minutes. An appropriate amount of purified water dissolving therein glycine and disodium hydrogenphosphate was further added and kneaded. The resulting mixture was dried in a fluidized drier at 50°C for 30 minutes. Thereafter, granules of 14~24 meshes were obtained by the use of a sieve.

Omeprazole	5.0 mg
Glycine	2.5 mg
Na ₂ HPO ₄ · 12H ₂ O	2.5 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.5 mg
Total	75.0 mg

Example 4-2

The composition of the formulation given below was made

into granules according to Example 4-1. The sodium L-glutamate and sodium pyrophosphate dissolved in purified water were incorporated.

Omeprazole	5.0 mg
Sodium L-glutamate	2.5 mg
Sodium pyrophosphate	1.0 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.5 mg
Total	75.0 mg

Example 4-3

From the composition given below, granules were produced according to Example 4-1. The L-alanine and dipotassium hydrogenphosphate were incorporated by dissolving them in purified water.

Omeprazole	5.0 mg
L-alanine	1.5 mg
K ₂ HPO ₄	1.5 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.5 mg
Total	75.0 mg

Example 4-4

The granules obtained in Example 4-3 were applied with coatings of the compositions given below to give enteric granules. Undercoatings 1, 2 were applied in a fluidized bed

drier (Okawara Co.) at an air feed temperature of 75°C and an exhaust temperature of 55°C and Enteric coating was applied similarly at an air feed temperature of 65°C and an exhaust temperature of 50°C.

Granules in Example 4-3	75.0 mg
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Undercoating 1

Hydroxypropylmethylcellulose phthalate	3.5 mg
Synthetic talcite	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg

Enteric coating

Hydroxypropylmethylcellulose	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg
Aggregate	100.0 mg

Example 4-5

Of the composition given below, omeprazole, mannitol,

sodium carboxymethylstarch, sodium laurylsulfate and hydroxypropylcellulose were mixed uniformly. An appropriate amount of purified water dissolving therein L-isoleucine and sodium pyrophosphate was added to the mixture and kneaded together, and then dried in a fluidized drier at 50°C for 30 minutes. The dried particles were passed through a sieve of 24 mesh and mixed with magnesium stearate, and then produced into tablets (core tablets) of 135 mg per one tablet by means of a rotary tableting machine.

Omeprazole	20.0 mg
L-Isoleucine	3.0 mg
Sodium pyrophosphate	3.0 mg
Mannitol	99.2 mg
Sodium carboxymethylstarch	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

Example 4-6

The tablets (core tablets) obtained in Example 4-5 were applied with coatings of the compositions given below to yield enteric tablets. Undercoatings 1, 2 were applied by means of High-coater (Freund Sangyo Co.) at an air feed temperature of 70°C and an exhaust temperature of 40°C, at a pan revolution number of 13 rpm. Enteric coating was likewise applied at an air feed temperature of 55°C and an exhaust temperature of 37 °C.

Tablets in Example 4-5	135.0 mg
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Undercoating 1

Hydroxypropylmethylcellulose	1.5 mg
Aluminum hydroxide•sodium bicarbonate coprecipitate	0.4 mg
Purified water	(23.0 mg)
Total	1.9 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg

Enteric coating

Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Total	3.5 mg
Aggregate	144.5 mg

Example 4-7

Core granules were produced according to Example 4-1 from the composition given below. The glycine and sodium pyrophosphate as a stabilizer was incorporated by dissolving them in purified water. In order to prevent an adverse effect of proton released from the enteric film upon omeprazole, aluminum hydroxide •sodium bicarbonate coprecipitate and disodium hydrogenphosphate were incorporated. Coating was conducted by the use of a fluidized bed drier (Okawara Co.). Undercoatings 1 and 2 were applied at an air feed temperature

of 75°C and an exhaust temperature of 55°C while Enteric coating was applied at an air feed temperature of 55°C and an exhaust temperature of 40°C.

Core granules

Omeprazole	5.0 mg
Glycine	2.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low substituted hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	52.5 mg
Total	70.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	3.2 mg
Aluminum hydroxide-sodium bicarbonate coprecipitate	1.2 mg
Na ₂ HPO ₄ · 12H ₂ O	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)
Total	5.0 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg
Purified water	(65.0 mg)
Total	5.0 mg

Enteric coating

Methacrylic acid/acrylic acid copolymer (solid)	15.0 mg
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Polyethylene glycol 6000	1.3 mg
Tween 80	0.7 mg
Talc	3.0 mg
Purified water	(50.0 mg)
Total	20.0 mg
Aggregate	100.0 mg

Experimental Example 4-2

Tablets (core tablets) were produced in the formulation given below according to Example 4-5 (Sample B).

Omeprazole	20.0 mg
Glycine	10.0 mg
Na ₂ HPO ₄ · 12H ₂ O	2.0 mg
Mannitol	87.5 mg
Carboxymethylcellulose	10.0 mg
Magnesium stearate	0.5 mg
Total	130.0 mg

Tablets (core) containing no stabilizer were produced in the formulation below according to Example 4-5 (Control B).

Omeprazol	20.0 mg
Mannitol	99.5 mg
Carboxymethylcellulose	10.0 mg
Magnesium stearate	0.5 mg
Total	130.0 mg

Sample B and Control B were preserved under 40°C, 75% RH for 4 weeks and measured of the change in appearance with a colorimeter to determine ΔE values. The results obtained are shown below.

Preparation	ΔE
Sample B	8.2
Control B	14.7

As will be apparent from above, no stabilization effect was obtained when amino acid, an acid salt of an amino acid or an alkali salt of an amino acid or a buffer was singly incorporated in omeprazole but when the aforementioned amino acid or the like and the buffer are used in admixture, omeprazole were significantly stabilized, whereby a stabilized preparation containing an antiulcer agent was obtained.

[Industrial Applicability]

The pharmaceutical preparations of this invention exhibit a superior inhibitory activity to secretion of gastric acid and superior antiulcer activity and can be used for the treatment of digestive ulcers, etc. of human or other mammals.

CLAIMS

1. An enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound that has antiulcer activity and is unstable to acid, an undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating, wherein said core portion and/or said undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide • sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an amino acid and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer.
2. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide • sodium bicarbonate coprecipitate.
3. The enteric pharmaceutical composition as set forth in item 2, wherein the aluminum hydroxide • sodium bicarbonate coprecipitate in the undercoating is in the range of 0.01~10

parts by weight based on 100 parts by weight of the core portion.

4. The enteric pharmaceutical composition as set forth in item 2, wherein the undercoating comprises aluminum hydroxide . sodium bicarbonate coprecipitate and talc.

5. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum hydroxide . sodium bicarbonate coprecipitate and a buffer.

6. The enteric pharmaceutical composition as set forth in item 5, wherein the aluminum hydroxide . sodium bicarbonate coprecipitate and a buffer are in the range of, respectively, 0.01~0.5 part by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound.

7. The enteric pharmaceutical composition as set forth in item 5, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate.

8. An enteric pharmaceutical composition improved in stability

and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise aluminum glycinate and a buffer.

9. The enteric pharmaceutical composition as set forth in item 8, wherein the aluminum glycinate and the buffer are in the range of, respectively, 0.1~2 parts by weight and 0.01~2 parts by weight based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound.

10. The enteric pharmaceutical composition as set forth in item 8, wherein the buffer is sodium tartarate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate or tripotassium phosphate.

11. An enteric pharmaceutical composition improved in stability and unchanged in dissolution property with the lapse of time, which composition comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to an acid, an undercoating of one or two layers covering the core portion, and an enteric coating further covering the undercoating, wherein the core portion and/or the undercoating comprise a mixture of an amino

acid, an acid salt of an amino acid or an alkali salt of an amino acid and a buffer.

12. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid, or alkali salt of an amino acid is in the range of 0.01~2 parts by weight and the buffer is in the range of 0.01~2 parts by weight, respectively, based on 1 part by weight of the 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound.

13. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonin, DL-threonin, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, sodium L-glutamate, L-asparagic acid, sodium L-asparagate, L-lysine or L-lysine-L-glutamate; and the buffer is an alkaline metal salt of phosphoric acid, sodium tartarate, sodium acetate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate or calcium carbonate.

14. The enteric pharmaceutical composition as set forth in item 11, wherein the amino acid, acid salt of an amino acid or alkali salt of an amino acid is glycine, L-alanine, DL-alanine or sodium L-glutamate; and the buffer is disodium hydrogenphosphate.

DRAWINGS

Fig. 1

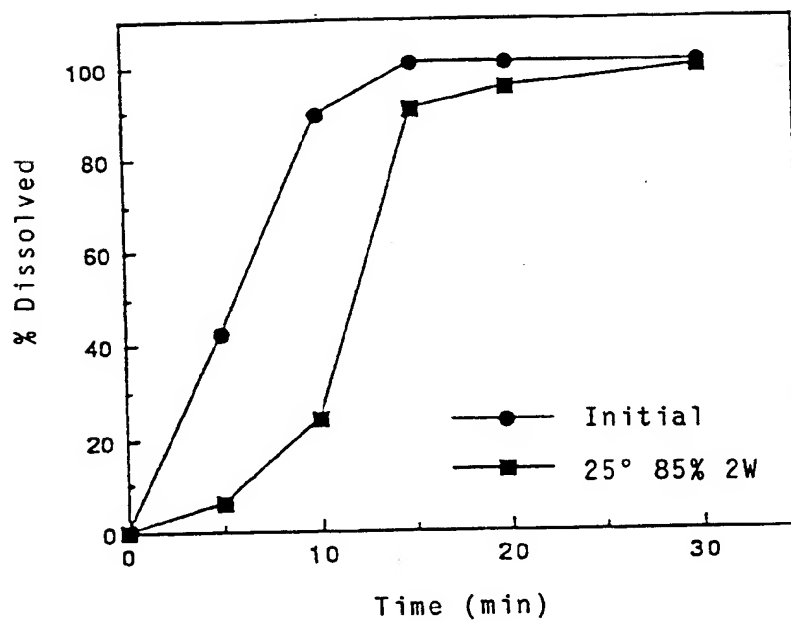


Fig. 2

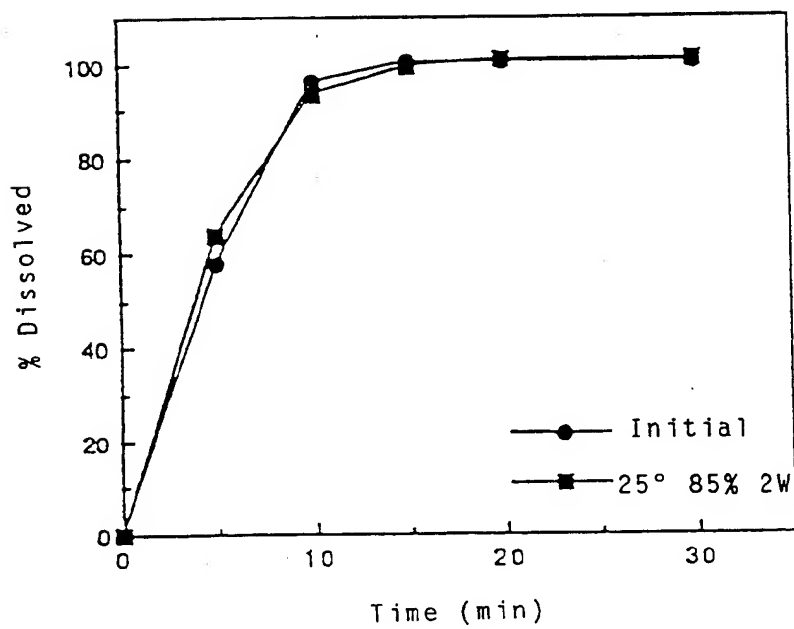


Fig. 3

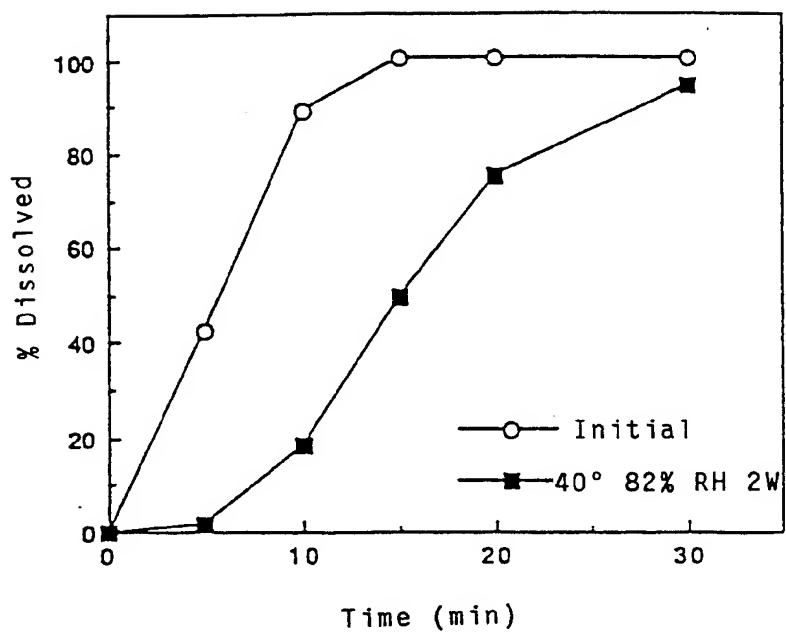


Fig. 4

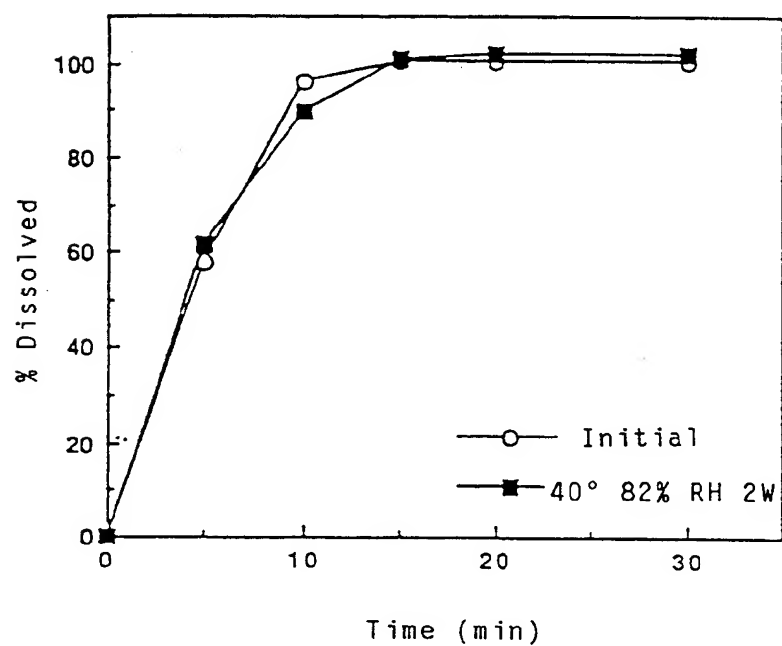
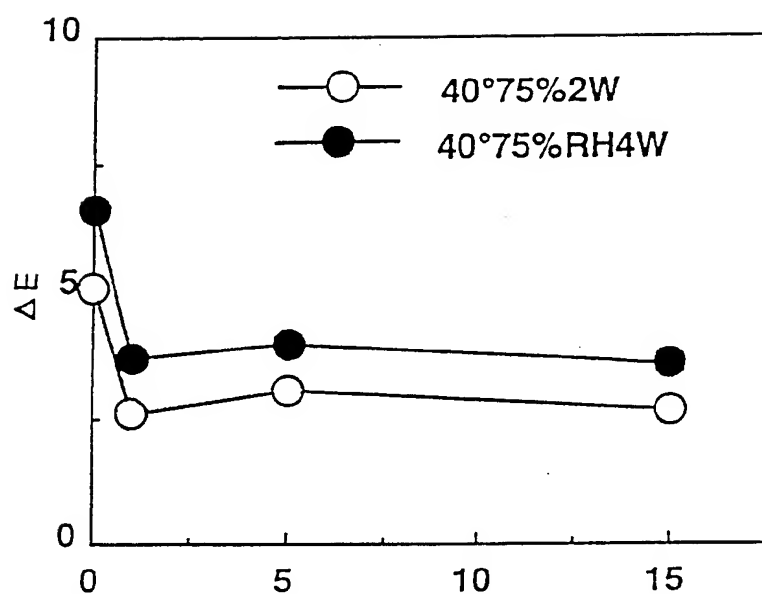


Fig. 5



additive amount of aluminum hydroxide · sodium
bicarbonate coprecipitate (mg/135 mg)

Fig. 6

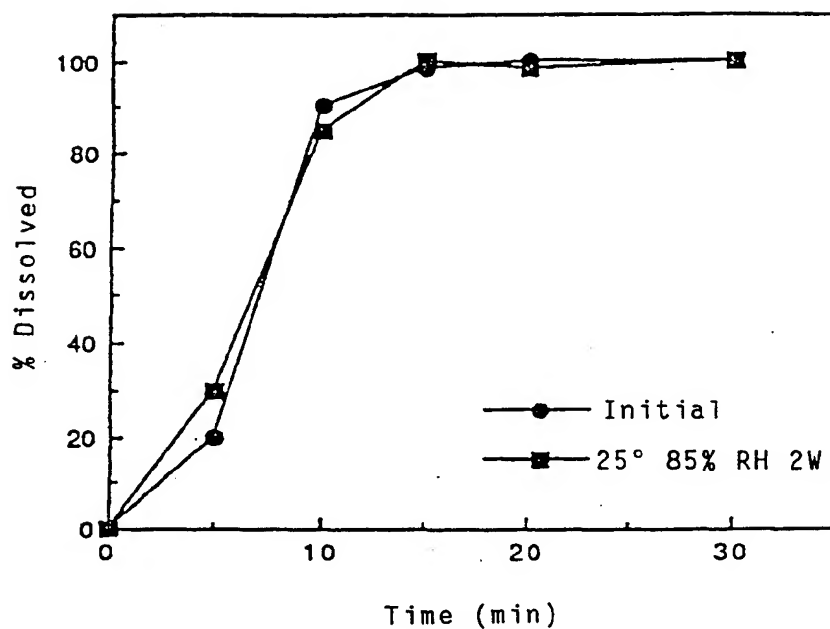
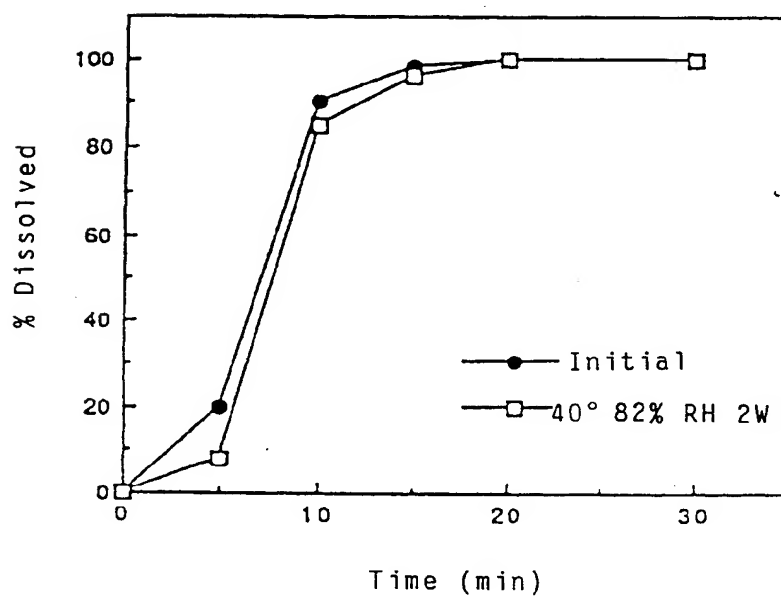


Fig. 7



INTERNATIONAL SEARCH REPORT

PCT/JP 93/00920

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K31/44; A61K9/28; A61K9/50		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0 248 634 (NIPPON CHEMIPHAR CO. LTD.) 9 December 1987 cited in the application see page 5, line 35 - page 6, line 23; claims 1-23 ---	1-14
Y	EP,A,0 237 200 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 16 September 1987 cited in the application see page 8, line 1 - line 58; examples 7,9 ---	1-14
Y	EP,A,0 247 983 (AKTIEBOLAGET HÄSSLE) 2 December 1987 cited in the application see page 5 - page 8; claims 1-12 ---	1-14
	-/--	
¹⁰ Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 13 MND_NAME 1993	Date of Mailing of this International Search Report 28. 10. 93	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer TZSCHOPPE D. A.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	ES,A,2 024 993 (CENTRO GENESIS PARA LA INVESTIGACION S.L.) 1 March 1992 see the whole document -----	1-14
P,Y	Week 3293, Derwent Publications Ltd., London, GB; AN 93-255964 & KR,A,9 208 161 (HAN MI PHARM. IND. CO) 24 September 1992 see abstract -----	1-14

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9300920
SA 75874

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0248634	09-12-87	JP-A- 62283964	09-12-87
		JP-A- 62283965	09-12-87
		JP-A- 63014773	21-01-88
		AU-A- 1858192	24-09-92
		AU-B- 619444	30-01-92
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EP-A-0237200	16-09-87	DE-A- 3780045	06-08-92
		EP-A- 0423748	24-04-91
		EP-A- 0446961	18-09-91
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		DE-A- 3783394	18-02-93
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		JP-A- 62258320	10-11-87
		US-A- 4786505	22-11-88
ES-A-2024993		None	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : A61K 31/44, 9/28, 9/50</p>	<p>A1</p>	<p>(11) International Publication Number: WO 94/02140 (43) International Publication Date: 3 February 1994 (03.02.94)</p>
<p>(21) International Application Number: PCT/JP93/00920 (22) International Filing Date: 2 July 1993 (02.07.93) (30) Priority data: 4/213436 17 July 1992 (17.07.92) JP 5/143028 20 May 1993 (20.05.93) JP (71) Applicant (for all designated States except US): YOSHITO- MI PHARMACEUTICAL INDUSTRIES, LTD. [JP/ JP]; 6-9, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only) : OISHI, Naohiro [JP/ JP]; SHIBATA, Toshiyuki [JP/JP]; IKEDA, Kuniki [JP/ JP]; Yoshitomi Pharmaceutical Industries, Ltd., Yoshito- mi Factory, 955, Oaza-Koiwai, Yoshitomimachi, Chiku- jo-gun, Fukuoka 871 (JP). (74) Agent: TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p>		<p>(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i></p>
<p>(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING ANTIULCER AGENT</p>		
<p>(57) Abstract An enteric pharmaceutical composition, containing antiulcer agent, improved in stability and unchanged in dissolution property with the lapse of time is provided, which comprises a core portion including a 2-[(2-pyridyl)methylsulfinyl] benzimidazole compound that has antiulcer activity and is unstable to acid, an undercoating of one or two layers covering the core portion and an enteric coating further covering the undercoating. The core portion and/or the undercoating comprise a stabilizer selected from the group consisting of aluminum hydroxide-sodium bicarbonate coprecipitate alone, a mixture of the aforementioned coprecipitate and a buffer e.g. disodium hydrogenphosphate.</p>		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/44, 9/08	A1	(11) International Publication Number: WO 94/02141 (43) International Publication Date: 3 February 1994 (03.02.94)
(21) International Application Number: PCT/JP93/00998 (22) International Filing Date: 15 July 1993 (15.07.93) (30) Priority data: 4/201203 28 July 1992 (28.07.92) JP (71) Applicants (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD. [JP/JP]; 6-9, Hiranomachi 2-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only) : NAKANISHI, Shigeo [JP/JP]; 12-5, Shimokidacho, Neyagawa-shi, Osaka 572 (JP). TOMINAGA, Tetsuo [JP/JP]; B-806, Kasugaoka-Abankonfoto, 136-3, Kasugaoka 2-chome, Itami-shi, Hyogo 664 (JP). YAMANATA, Iwao [JP/JP]; 5-6-12, Kami-minami, Hirano-ku, Osaka-shi, Osaka 547 (JP). HIGO, Takashi [JP/JP]; 2-2-10, Midorigaoka, Ikeda-shi, Osaka 563 (JP). SHIBATA, Toshiyuki [JP/JP]; 774-105, Oaza-Higashihama, Nakatsu-shi, Oita 871 (JP).		(74) Agent: TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS (57) Abstract <p>An injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5, and an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is 9.5 - 11.5: (a): a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or salt thereof having antiulcer activity; (b): an aqueous solvent added with no nonaqueous solvent. The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.</p>		

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SPECIFICATION

INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS

[TECHNICAL FIELD]

The present invention relates to an injection of 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, particularly sodium salt of omeprazole and to an injection kit thereof, which are used in clinical fields.

[BACKGROUND ART]

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds such as omeprazole or lansoprazole are potent antiulcer agents, and are used as pharmaceutical compositions for oral administration. Further, the injections thereof have recently developed.

As an injection of omeprazole, there has been known an injection prepared by dissolving sodium salt of omeprazole in sterilized water, filtering and lyophilizing the solution to give a lyophilized product, and then dissolving the lyophilized product in a mixture of polyethylene glycol 400 for injection, sodium dihydrogenphosphate and sterilized water (Japanese Patent Unexamined Publication No. 167587/1984).

Also, an injection prepared by dissolving a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound having antiulcer activity such as lansoprazole in a mixture of (a) acid, and (b) at least one of ethanol, propylene glycol and polyethylene glycol

(Japanese Patent Unexamined Publication No. 138213/1990).

In general, the pH of injection is preferably about 4-8, and a pH above 9 has a probability of causing hemolysis and local irritation.

In the case of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt which may be hereinafter referred to as "benzimidazole compound or salt thereof" represented by sodium salt of omeprazole, it shows a solubility of the level permitting formulation into preparation, in water in an alkaline range of pH 9.5 or above, whereas it shows extremely low solubility in water at a pH of not more than 9, thus rendering formulation into preparation very difficult.

While the benzimidazole compound or salt thereof is stable in the alkaline range, it poses a problem in that its stability decreases with the lowering pHs.

For this reason, it has been employed in conventional injections of benzimidazole compound or salt thereof such as sodium salt of omeprazole to add an acid such as hydrochloric acid or sodium dihydrogenphosphate to the solution to keep the pH from neutral to weak basic, and to further add a nonaqueous solvent such as polyethylene glycol, ethanol or propylene glycol in order to obtain a certain level of solubility in such pH range.

Yet, these injections pose problems of local irritation and hemolysis caused by the nonaqueous solvent added to the solution for dissolution.

Accordingly, an object of the invention is to provide an injection of benzimidazole compound or salt thereof, particularly sodium salt of omeprazole causing less side-effects such as hemolysis, and less local irritation, which permits easy formulation.

[DISCLOSURE OF THE INVENTION]

As a result of the intensive study conducted by the inventors with the aim of achieving the aforementioned object, it has now been found that a product obtained by lyophilizing an alkaline aqueous solution of benzimidazole compound or salt thereof, and dissolving same in an aqueous solvent added with no nonaqueous solvent scarcely shows hemolytic property and local irritation, notwithstanding the high pH of from 9.5 to 11.5.

Accordingly, the present invention is:

- (1) an injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, which has a pH of not less than 9.5 and not more than 11.5,
- (2) an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;
(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt

thereof having antiulcer activity

(b) : an aqueous solvent added with no nonaqueous solvent.

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds having antiulcer activity which are the element constituting the present invention include, for example, the compounds described in Japanese Patent Unexamined Publication No. 62275/1977, Japanese Patent Unexamined Publication No. 1417/1979, Japanese Patent Unexamined Publication No. 53406/1982, Japanese Patent Unexamined Publication No. 135881/1983, Japanese Patent Unexamined Publication No. 192880/1983, Japanese Patent Unexamined Publication No. 181277/1984 or Japanese Patent Unexamined Publication No. 50978/1986, and omeprazole [chemical name: 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole] and lansoprazole [chemical name: 2-{2-[(3-methyl-4-(2,2,2-trifluoroethoxy)]-pyridylmethylsulfinyl} - benzimidazole] are exemplified.

As the salts of said benzimidazole compounds, for example, salts of alkaline metal such as sodium salt or potassium salt or salts of alkaline earth metal such as calcium salt or magnesium salt.

In view of the solubility, it is preferable for the present invention to use the salt of benzimidazole compound.

The injection of the present invention has a pH of not less than 9.5 and not more than 11.5, preferably not less than 10 and not more than 11. Where the pH is less than 9.5, the benzimidazole compound or salt thereof does not sufficiently

dissolve in an aqueous solvent and shows poor stability, while where it is more than 11.5, hemolytic property and local irritation become prominent.

According to the present invention, an injection of the benzimidazole compound or salt thereof can be prepared by dissolving the benzimidazole compound or salt thereof in water for injection, etc. along with a strong alkaline compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or L-arginine, to give an alkaline aqueous solution having a pH adjusted to not less than 10.5 and not more than 12.5, preferably not less than 11 and not more than 12. The alkaline aqueous solution may contain mannitol, glycine, sorbitol, inositol, etc. on demand for better forming of a lyophilized product.

The benzimidazole compound is contained in said alkaline aqueous solution in a proportion of 1-50 mg/ml, preferably 5-40 mg/ml on a free compound basis.

Then, this alkaline aqueous solution is filtered for sterilization, and charged in a vial by 0.5-10 ml. After nitrogen gas displacement to be conducted as necessary, the solution is lyophilized by a method known per se. The lyophilized product thus obtained is the (a): a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compounds or salt thereof having antiulcer activity to be contained in the injection kit of the present invention.

When in use, the injection of the present invention can be produced by dissolving the lyophilized product thus obtained in an aqueous solvent added with no nonaqueous solvent, such as physiological saline, aqueous solution of 5% glucose, or distilled water for injection. Said aqueous solvent corresponds to the (b) : an aqueous solvent added with no nonaqueous solvent to be contained in the injection kit of the present invention.

The injection of the present invention can be used, for example, in the form of drip infusion, intravenous injection, intramuscular injection, subcutaneous injection.

The concentration of benzimidazole compound in the injection of the present invention may vary depending upon the administration route, and generally ranges in a proportion of 0.05-10 mg/ml, preferably 0.1-5 mg/ml on a free compound basis.

The benzimidazole compound in the injection of the present invention is administered to an adult at 10-100 mg per day on a free compound basis in a single to three times divided doses, depending upon, for example, the symptoms of the patients.

[BEST MODE FOR CARRYING OUT OF THE INVENTION]

Experimental Example 1

Test preparation

1. Preparation obtained in Example 1 to be mentioned later

Test method

1. Hemolysis test

Hemolysis was evaluated by Akaishi method using whole blood

of rabbit. The result is given in Table 1.

2. Local irritation test

Local irritation was evaluated by the comparison of necrotic muscular tissue area at the injection site in 3 rabbits at 2 days after the administration of 1 ml of the test preparation by intramuscular injection, with that in the rabbits administered with 1 ml of physiological saline or 1 ml of a 1.7% acetic acid solution, respectively by intramuscular injection.

The results are summarized in Table 2.

Test results

Table 1

Test preparation	pH	Hemolysis
Ex. 1	10.5	not observed

Table 2

Test preparation	pH	Necrotic area (mm ²)
Ex. 1	10.5	63
1.7% acetic acid solution (positive comparison solution)	—	398
physiological saline (negative comparison solution)	—	31

(average of 3 rabbits)

The preparation of the present invention is desirable as an injection, since it does not cause hemolysis at all despite the high pH, and causes less local irritation.

Example 1

1N Sodium hydroxide (2.3 ml) is added to 21.3 g of sodium salt of omeprazole (20 g as omeprazole), and water for injection is added thereto to adjust the pH to 11.5 and the total amount to 1 kg.

After filtration for sterilization, this alkaline aqueous solution is charged in 10 ml vials by 2 g. A rubber plug is half driven in, and nitrogen displacement is performed.

Lyophilization by a conventional method and dissolution of the lyophilized product obtained in 10 ml of physiological saline give an omeprazole injection [4 mg (free compound)/ml].

[INDUSTRIAL APPLICABILITY]

The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent such as polyethylene glycol to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. As a result, irritation and hemolysis caused by the nonaqueous solvent can be avoided. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

CLAIMS

1. An injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5.

2. The injection of Claim 1, prepared by dissolving a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity in the aqueous solvent added with no nonaqueous solvent.

3. An injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;

(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity

(b) : an aqueous solvent added with no nonaqueous solvent.

4. The injection of Claim 1 or 2, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof is sodium salt of omeprazole.

5. The injection kit of Claim 3, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or the salt thereof is sodium salt of omeprazole.

INTERNATIONAL SEARCH REPORT

PCT/JP 93/00998

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
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II. FIELDS SEARCHED		
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Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 382 489 (TAKEDA) 16 August 1990 see claims see page 7, line 50 - line 52 see example 2 ---	1-5
A	EP,A,0 124 495 (AKTIEBOLAGET HÄSSLE) 7 November 1984 cited in the application see claims see page 6, line 6 - line 15 see page 7, line 31 - line 37 see page 8, line 1 - line 8 see example 13 ---	1-5
A	EP,A,0 356 143 (TAKEDA) 28 February 1990 cited in the application see claims -----	1-5
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
29 SEPTEMBER 1993		07.10.93
International Searching Authority		Signature of Authorized Officer
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

JP 9300998
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(21) International Application Number: PCT/SE94/00681 (22) International Filing Date: 8 July 1994 (08.07.94) (30) Priority Data: 9302395-0 9 July 1993 (09.07.93) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BENGTTSSON, Inga, Siv [SE/SE]; Klintens väg 13, S-414 76 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: LARSSON, Birgitta; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i>
(54) Title: NEW PHARMACEUTICAL FORMULATION (57) Abstract A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.		

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NEW PHARMACEUTICAL FORMULATION

5 Field of the invention

The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in
10 medicine.

Background of the invention

The compound known under the generic name omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described
15 i.a. in EP-A 0 005 129.

Omeprazole is useful for inhibiting gastric acid secretion and has gastric mucosa protective activity. In a more general sense, omeprazole may be used for
20 prevention and treatment of gastric acid related disorders in mammals and man, including e.g. gastroesophageal reflux disease, gastritis, gastric ulcer and duodenal ulcer. Omeprazole is susceptible to degradation/transformation in acid reacting and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values
25 degradation proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Omeprazole also in the solid state is susceptible to degradation and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also
30 affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid
5 absorption of omeprazole can occur.

A pharmaceutical oral solid dosage form of omeprazole must be protected from contact with acidic gastric juice by an enteric coating. In US-A 4,786,505 is described an enteric coated omeprazole preparation containing a separating subcoat
10 between the core material and the enteric coating. Said preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

Certain salts of omeprazole including alkaline reacting salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and
15 importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a
20 strong desire for the use of water based processes in production of pharmaceutical products.

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that
25 the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less attractive in full scale production. Performing the process without crystallization of the magnesium omeprazole gives a product which is less suitable as a pharmaceutical substance.

30 In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that

said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

5 The combination of physical properties of the novel magnesium omeprazole product described in the present specification with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is useful for the manufacture of the new pharmaceutical formulation.

10

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

15 Description of the invention

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

20 Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and has a good stability during long-term storage.

25

Yet another object of the invention is to provide an environmental friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

30 The new dosage form is characterized in the following way. Core material in the form of pellets, granules or tablets containing the novel form of a magnesium salt of omeprazole, optionally together with an alkaline reacting compound, and on said

core material one or more subcoating layers optionally comprising tablet excipients which are soluble or insoluble but disintegrating in water, or polymeric, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the core and an outer layer, which is an enteric coating. This/these inner
5 layer/layers separates/separate the core material from the outer layer being an enteric coating.

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step, which usually is carried out using an organic
10 solvent, can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity
15 which is higher than 70% is useful in the manufacture of the pharmaceutical formulations of omeprazole according to the present invention.

Detailed description of the invention

20 The new pharmaceutical formulation is defined in claims 1-8, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in claims 9-10 and the use of the formulation in medicine is defined in claims 11-17.

25 Magnesium omeprazole

Magnesium omeprazole feasible for the manufacturing of the claimed formulation has the following properties:

- 30 a) Crystalline form, with a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

It is desirable that the product also exhibits the following properties;

- 5 b) Particle size measured as mean mass diameter (MMD) less than 30 μm , preferably less than 20 μm as determined by laser diffraction technique.
- c) Density between 1.33 g/cm^3 and 1.35 g/cm^3 as determined by powder pycnometer.
- 10 d) Hygroscopicity not exceeding 2% increase of weight upon storage for one month up to 94% relative atmospheric humidity as determined gravimetrically.
- 15 e) A content of water of between 5% and 10% by weight as determined by titration according to Karl Fischer.
- f) A content of methanol less than 0.1% preferably less than 0.05% by weight as determined by gas chromatography, in case methanol is used as solvent.
- 20 The process for producing the novel form of magnesium omeprazole is characterized by the following consecutive steps
- 1) treating omeprazole or a salt thereof with magnesium alcoholate in a solution
- 25 2) separating inorganic salts from the reaction mixture
- 3) crystallizing magnesium omeprazole
- 4) isolating the obtained crystalline magnesium omeprazole and, optionally
- 30 5) purifying and drying the crystalline magnesium omeprazole using conventional methods.

The process for manufacturing the novel magnesium omeprazole can be described in the following way:

5 A lower alcohol, such as methanol, ethanol, n-propanol or iso-propanol, preferably methanol, is treated in a solution of polar solvents with a weighed amount of magnesium at temperatures between 0°C and reflux temperature. The temperature should preferably be between 10 and 30°C. After addition of the magnesium to the solution the temperature can, in a second step be raised further to between 0°C and reflux temperature, preferably 20-50°C. After termination of the reaction the
10 temperature is reduced to 0-40°C, preferably 10-25°C. Omeprazole or a salt of omeprazole is then added to the solution and after termination of the reaction the mixture is cooled to -10°C to +20°C, preferably -5°C to +5°C. The solvent is then evaporated to 40-60% of the initial volume, which makes the inorganic salts precipitate. The precipitate is separated from the reaction solution for example by
15 centrifugation or filtration and the solution is heated to 5°C to 30°C whereafter the solution is seeded with magnesium omeprazole crystals. An amount of water, which is approximately equal to the volume of the solution, is added to start the crystallization. The solution is cooled to -10 to +20°C, preferably 0-10°C to complete the crystallization. The crystals are then separated from the mother liquid
20 for example by centrifugation or filtration and washed with polar solvents preferably an aqueous lower alcohol such as aqueous methanol. Finally, the crystals are dried preferably under reduced pressure and heating.

25 Pharmaceutical formulations containing the novel magnesium omeprazole described above are manufactured as described herein below.

Core material

30 The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture. Optionally the magnesium omeprazole may be mixed with an

alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules or tablets, by conventional pharmaceutical procedures. The pellets, granules or tablets are used as core material for further processing.

Separating layer - subcoating.

The cores containing magnesium omeprazole and optionally alkaline reacting substances are separated from the enteric coating polymer(s). The subcoating layer, in the following defined as the separating layer, serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the core can react with hydroxyl ions diffusing from the core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and

aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids or salts thereof.

- 5 The separating layer may consist of one or more layers.

The separating layer(s) can be applied to the core material - pellets, granules or tablets - by conventional coating procedures in a suitable coating pan, centrifugal fluidized coating-granulator, or in a fluidized bed apparatus using water and/or
10 conventional organic solvents for the coating solution. The material for the separating layer is chosen among pharmaceutically acceptable, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxymethyl cellulose or
15 hydroxypropyl methylcellulose. The separating layer, "subcoating", applied to the core material may constitute from approximately 0.5 to 25 % by weight of the core weight, preferably 2.0 - 10.0 %, and more preferably 2.5 - 5.0 %.

In the case of a tablet formulation another method to apply the separating layer(s)
20 can be performed by drycoating technique. First a tablet containing magnesium omeprazole is formulated as described above. Around this tablet one or more layers are compressed using a suitable tableting machine. The separating layer(s) consists of pharmaceutically acceptable, soluble or insoluble but in water disintegrating tablet excipients. The separating layer(s) has preferably a thickness of not less than
25 approximately 1 mm.

Ordinary plasticizers, colorants, pigments, titanium dioxide, talc and other additives may also be included into one or more of the separating layer(s).

Enteric coating layer

- The enteric coating layer is applied in one or more layers onto the subcoated core material by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known under the trade names Aquateric® (FMC Corporation), Eudragit® (Röhm Pharma), Acoat™ (Shin-Etsu Chemical), Opadry™ (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-50 % of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.
- The thickness of the enteric coating may vary widely without influencing the in vitro release of omeprazole in test solutions which mimic in vivo conditions in man. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0 % by weight of the core weight, preferably at least 3.0 % and especially at least 6.0 %. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to vary the thickness of the enteric coating without deleterious influence on the release of omeprazole is

especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation containing subcoating layer(s) without exactly controlling the thickness of the applied coating layer(s).

- 5 Thus, the formulation according to the invention consists of core material containing magnesium omeprazole optionally mixed with alkaline reacting compound(s). The addition of alkaline reacting material is not necessary, in any sense, but such a substance may further enhance the stability of omeprazole. The core material is coated with an enteric coating rendering the dosage form insoluble
10 in acid media, but disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted. The core material is further coated with an soluble or insoluble but in water disintegrating coating, optionally containing one or more pH-buffering substances, which separate the core material from the enteric coating.

15

Final dosage form

- The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets or granules, these pellets or granules dispensed in hard
20 gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colorant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules or pellets) is kept low.

25

Process

- A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material, said material is first coated with the separating layer(s) and then with the enteric
30 coating layer(s). The coating(s) are carried out as described above. Further another

aspect of the invention is that the pharmaceutical processes can be completely water-based.

5 The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

10 The invention is illustrated in detail by the following examples. Example 1 discloses the preparation of the novel magnesium omeprazole product, which product is suitable in manufacturing of the pharmaceutical formulations according to the present invention. Example 2 discloses compositions of different enteric coated tablets containing magnesium omeprazole and results from acid resistance
15 test and in vitro dissolution test. Examples 3 discloses tablet formulations with different thickness of the enteric coating, the obtained gastric acid resistance of said formulations and the in vitro release rate of omeprazole. Example 4 discloses an enteric coated pellet formulation.

20 Examples

The following detailed Example 1 will serve to illustrate a process for manufacturing the magnesium omeprazole, which will be used in the pharmaceutical preparations according to the present invention.

25

Example 1

A reactor was filled with 2026 litres of methanol. The stirrer was started and the temperature was adjusted to 20°C. 3,90 kg of magnesium was added to the vessel
30 and immediately thereafter 1,0 litre of CH₂Cl₂. The reactor was heated to 40°C and kept at this temperature for 60 min. It was then cooled to 15°C before the addition of 99,9 kg of omeprazole. The reactor was kept at this temperature for

60 min and then cooled to 0°C. The temperature was kept at this level for 30 minutes before 1000 L of methanol were evaporated under vacuum and the inorganic solid salt was separated from the liquid first by centrifugation and then by filtration. The liquid was heated to 10°C and the liquid was seeded with
 5 magnesium omeprazole crystals whereafter the magnesium omeprazole salt was precipitated by addition of 900 L of water. The mixture was then cooled to 5°C. After the crystallization had been completed the magnesium omeprazole crystals were centrifuged off and then washed with a mixture of 50 L of methanol and 150 L of water. The produced magnesium omeprazole was dried under reduced pressure
 10 finally producing 92,5 kg of crystalline product corresponding to a yield of 81,4%.

The novel form of the magnesium salt of omeprazole according to Example 1 fulfills the properties defined above.

15 Example 2

Tablet formulations containing magnesium omeprazole.

	Amount omeprazole	10	20	40
20	Ingredient	(mg/tabl)	(mg/tabl)	(mg/tabl)

Tablet core

	Magnesium omeprazole	11.2	22.5	45.0
25	Mannitol	68.7	57.4	34.9
	Microcrystalline cellulose	25.0	25.0	25.0
	Sodium starch glycolate	6.0	6.0	6.0
	Hydroxypropyl methylcellulose	6.0	6.0	6.0
	Talc	5.0	5.0	5.0
30	Sodium stearyl fumarate	2.5	2.5	2.5
	Water purified	50.0	50.0	50.0

Sub-coating layer

	Hydroxypropyl methylcellulose	3.7	3.7	3.7
	Hydrogen peroxide 30%	0.04	0.04	0.04
5	Water purified	34.0	34.0	34.0

Enteric coating layer

	Methacrylic acid copolymer	9.1	9.1	9.1
10	Polyethylene glycol	1.0	1.0	1.0
	Titanium dioxide	0.82	1.1	0.51
	Colour iron oxide, red-brown	0.04	0.13	0.43
	Colour iron oxide, yellow	0.02	-	-
	Water purified	45.0	45.0	45.0

15

Polish

	Paraffin powder	0.05	0.05	0.05
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20 The tablets with an amount of 20 mg omeprazole/tablet have been manufactured both in a pilot scale of about 300 000 tablets and a large scale of about 2 million tablets.

Description of manufacturing

25

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are sub-coated with a polymer film based on hydroxypropyl methylcellulose and enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

30

Investigation of acid-resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

Tablet Strength (mg)	Acid resistance (%)	
10	95	(93-98)
20	100	(94-102)
40	100	(96-103)

15 Investigation of in-vitro dissolution

After exposure to acid environment, pH 1.2, as described above, the medium was switched to artificial intestinal fluid without enzymes, pH 6.8. The dissolved amount of omeprazole was determined by HPLC.

Tablet Strength (mg)	Dissolved amount of omeprazole (%) after (minutes)						
	0 (%)	5 (%)	10 (%)	15 (%)	20 (%)	25 (%)	30 (%)
10	0	2	78	92	93	94	94
20	0	0	75	93	96	96	97
40	0	9	71	86	91	91	94

All values of dissolved amount of omeprazole are mean values of 12 tablets.

Example 3

Tablet formulations containing magnesium omeprazole with different thickness of the enteric coating.

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The composition of the tablets is the same as in Example 2 (20 mg omeprazole). The tablets (n=6) have been exposed in an artificial gastric juice (pH 1.2) during 2 hours and then analysed for remaining amount of omeprazole (acid resistance). The release of omeprazole was analysed on tablets (n=6) pre-exposed in gastric

10

juice 2 hrs and thereafter exposed in a buffer solution (pH 6.8) during 30 min.

	Experiment ^{x)}	Enteric coating	Acid resistance	Release
		(% weight per tablet)	(% residue after 2h; pH 1.2)	(% after 30 min; pH 6.8)
	A	8	101 (98-105)	94 (93-96)
15	B	8	100 (98-102)	95 (85-98)
	C	16		98 (96-100)

^{x)} A manufactured in large scale
 B manufactured in pilot scale
 C manufactured in laboratory scale

20

Example 4

Enteric coated pellet formulation containing magnesium omeprazole.

25

Pellet core

	Magnesium omeprazole	225 g
	Mannitol	1425 g
30	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g

		16
	Lactose anhydrous	80 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate dihydrate	8 g
5	Water purified	350 g

Subcoating layer (I)

	Hydroxypropyl methylcellulose	70 g
10	Water purified	1450 g

Enteric-coating layer (II)

	Methacrylic acid copolymer	430 g
15	Polyethylene glycol	40 g
	Water purified	1890 g

Polish

20	Magnesium stearate	5 g
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The dry ingredients given above were mixed well in a mixer. Addition of granulation liquid was made and the mixture was kneaded and granulated to a proper consistency. The wet mass was pressed through an extruder and the granules
25 were converted to spherical form in a spheronizer. The pellets were dried and classified into suitable particle size ranges, e.g. 0.5-1.5 mm.

The polymer solution (I) was sprayed on the uncoated pellets in a fluidized bed apparatus under conditions suitable for the equipment used.

30

The polymer dispersion (II) was sprayed on the subcoated pellets in a fluidized bed apparatus. The enteric-coated pellets were classified, polishing material was

admixed and the pellets were filled into hard gelatin capsules in an amount corresponding to 20 mg of omeprazole, using a capsule filling machine.

Biopharmaceutical tests.

5

The enteric coated formulations according to Example 2 have been tested in humans with good results.

CLAIMS

1. An oral enteric coated formulation containing a core material of an active substance coated with one or more subcoating layers and one or more enteric coating layers **characterized in** that the core material as active substance contains a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction and optionally an alkaline reacting compound, on the core material applied subcoating layer(s), separating the core material from the enteric coating whereby the thickness of the enteric coating does not essentially influence the release of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.
2. A formulation according to claim 1, wherein the formulation is a tablet formulation.
3. A formulation according to claim 1, wherein the formulation is a pellet formulation.
4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.
5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate phthalate.
6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0 % by weight of the weight of the core material.

7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0 % by weight of the weight of the core material.
8. A formulation according to claim 1 wherein the subcoating layer(s) comprise
5 polymeric, filmforming compounds or tablet excipients which are soluble or insoluble but disintegrating in water, and optionally containing pH-buffering, alkaline compounds.
9. A formulation according to claim 1 wherein the produced enteric coated
10 formulation contains an overcoat, optionally comprising one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.
10. A process for the manufacture of a formulation according to claim 1 in which the core material containing magnesium omeprazole optionally mixed with an
15 alkaline reacting compound is coated with one or more subcoating layers, whereafter the subcoated core material is further coated with one or more enteric coating layers.
11. A process according to claim 10, wherein the subcoating layer(s) is applied
20 on the core material by a drycoating process.
12. An oral enteric coated formulation according to any of claims 1 to 9 for use in therapy.
13. An oral enteric coated formulation according to any of claims 1 to 9 for use
25 in inhibiting gastric acid secretion in mammals and man.
14. An oral enteric coated formulation according to any of claims 1 to 9 for use in the treatment of gastric acid related diseases in mammals and man.

15. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals and man.
- 5 16. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for treatment of gastric acid related diseases in mammals and man.
- 10 17. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.
- 15 18. A method for the treatment of gastric acid related diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00681

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/24, A61K 9/52, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0342522 (EISAI CO., LTD.), 23 November 1989 (23.11.89), page 2, line 34 - page 3, line 29, claims --	1-16
X	EP, A2, 0247983 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87), page 5, line 6 - page 9, line 12, claims --	1-16
A	EP, A2, 0124495 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.84) -- -----	1-16

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 October 1994

Date of mailing of the international search report

25 -10- 1994

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:
Methods for treatment of the human or animal body by surgery or therapy,
as well as diagnostic methods (see PCT Rule 39(iv)).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/10/94

International application No.

PCT/SE 94/00681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0342522	23/11/89	SE-T3- 0342522 DE-U- 6890056 ES-T- 2051919 JP-A- 1290628 US-A- 5035899	30/01/92 01/07/94 22/11/89 30/07/91
EP-A2- 0247983	02/12/87	SE-T3- 0247983 AU-B- 601974 AU-A- 7191287 CA-A- 1292693 DE-A- 3783394 EP-A- 0496437 EP-A- 0567201 ES-T- 2006457 GB-A- 2189698 JP-A- 5294831 JP-A- 62258320 NO-B- 174239 US-A- 4786505	27/09/90 05/11/87 03/12/91 18/02/93 29/07/92 27/10/93 01/01/94 04/11/87 09/11/93 10/11/87 27/12/93 22/11/88
EP-A2- 0124495	07/11/84	SE-T3- 0124495 AU-B- 563842 AU-A- 2525784 CA-A- 1264751 GB-A,B- 2137616 JP-C- 1651336 JP-B- 3013233 JP-A- 59167587 SU-A- 1314953 US-A- 4738974	23/07/87 06/09/84 23/01/90 10/10/84 30/03/92 22/02/91 21/09/84 30/05/87 19/04/88

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特許協力条約に基づいて公開された国際出願

(51) 国際特許分類 6 C07F 1/10, A01N 43/50	A1	(11) 国際公開番号 WO 95/07913 (43) 国際公開日 1995年3月23日 (23.03.95)
(21) 国際出願番号 PCT/JP94/01520 (22) 国際出願日 1994年9月14日 (14. 09. 94) (30) 優先権データ 特願平5/231218 1993年9月17日 (17. 09. 93) JP 特願平5/320076 1993年12月20日 (20. 12. 93) JP (71) 出願人 (米国を除くすべての指定国について) 明治乳業株式会社 (MEIJI MILK PRODUCTS CO., LTD.) [JP/JP] 〒104 東京都中央区京橋2丁目3番6号 Tokyo, (JP) (72) 発明者 : および (75) 発明者 / 出願人 (米国についてのみ) 小田宗宏 (ODA, Munehiro) [JP/JP] 須藤哲史 (SUDO, Tetsushi) [JP/JP] 佐久間貞俊 (SAKUMA, Sadatoshi) [JP/JP] 鈴木靖徳 (SUZUKI, Yasunori) [JP/JP] 〒250 神奈川県小田原市成田540 明治乳業株式会社 細胞工学センター内 Kanagawa, (JP) 伊藤裕之 (ITO, Hiroyuki) [JP/JP] 〒250 神奈川県小田原市成田540 明治乳業株式会社 ヘルスサイエンス研究所内 Kanagawa, (JP) 野宮健司 (NOMIYA, Kenji) [JP/JP] 〒257 神奈川県秦野市名古木390-6 Kanagawa, (JP)		(74) 代理人 弁理士 有賀三幸, 外 (ARUGA, Mitsuyuki et al.) 〒103 東京都中央区日本橋人形町1丁目3番6号 共同ビル Tokyo, (JP) (81) 指定国 JP, US, 欧州特許 (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). 添付公開書類 国際調査報告書
(54) Title : ANTIBACTERIAL AND ANTIFUNGAL AGENT (54) 発明の名称 抗菌抗かび剤 (57) Abstract A compound comprising a combination of imidazole or a derivative thereof with a silver ion; and an antibacterial and antifungal agent and an acaricidal agent each containing the above compound as the active ingredient. The agents have a wide antibacterial and antifungal spectrum, do not adversely affect the quality of the raw material, exhibit the activity unchanged for long, and are reduced in acute peroral toxicity, skin irritation and mucosa irritation.		

(57) 要約

本発明は、イミダゾール又はその誘導体と銀イオンとが結合してなる化合物及びこの化合物を有効成分とする抗菌抗かび剤、殺ダニ剤に関する。広範な抗菌抗かびスペクトルを有し、素材の品質に影響を及ぼさず、かつ、その作用が長期間にわたり持続するものであり、しかも急性経口毒性、皮膚刺激性、粘膜刺激性等が低い。

情報としての用途のみ

P C Tに基づいて公開される国際出願をパンフレット第一頁にP C T加盟国を同定するために使用されるコード

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DE	ドイツ	KZ	カザフスタン	PL	ポーランド		

明 細 書

抗菌抗かび剤

技術分野

本発明は抗菌抗かび剤及び殺ダニ剤に関し、更に詳しくは、広範な抗菌スペクトルを有するとともに耐久性、残効性等に優れ、しかも皮膚刺激性、粘膜刺激性等が低減された安全性の高い抗菌抗かび剤、及び殺ダニ剤に関する。

背景技術

近年、抗菌抗かび活性を有する薬剤をいろいろな生活関連用素材、例えば繊維、衛生加工品、食器、包装材料等の素材に適用して新たな機能を付与した機能性素材を開発する試みが多くなされている。これらの機能性素材は、抗菌抗かび活性を有する薬剤を該素材に添加し又は練り込むことにより、新たな機能を付与したものである。

これらの機能性素材分野へ向けて、抗菌抗かび剤の適用を図る際には、当該薬剤については広い範囲の抗菌抗かびスペクトルと安全性を有することが要求されるとともに、薬剤が素材の品質に影響を及ぼさないこと、耐久性、残効性、経済性などが要求される。

これまでに抗菌抗かび剤に使用されている薬剤としては、ベンゾイミダゾール系、ニトリル系、イソチアゾリン系、ハロアリルスルホン系、ヨードプロパルギル系、ベンゾチアゾール系、フェノール系、有機スズ系、ピリジン系、ジフェニルエーテル系、クロルヘキシジン系等が挙げられる。

しかし、これらの抗菌抗かび剤は、一種類の薬剤のみでは十分な抗菌抗かび効果を示し得ないものが多い。また、薬剤自体が示す抗菌抗かび活性が優れていても、素材との適合性という点で問題が生じ、素材への適用の際には、必ずしも十分な抗菌抗かび効果を示すとは限らない。一方、これら抗菌抗かび剤の安全性についてみると、急性経口毒性、皮膚刺激性、粘膜刺激性等を示すものが多く、これらの作用は、概して抗菌抗かび活性の強いものほど強く、このような抗菌抗かび剤を生活環境に適用することには問題があった。

そこで、広範な抗菌抗かびスペクトルを有するとともに、使用される素材に影

響を及ぼすことなく、耐久性、残効性等に優れ、しかも急性経口毒性、皮膚刺激性、粘膜刺激性等が低減された抗菌抗かび剤の開発が望まれていた。

一方、ダニは、気管支喘息やアレルギー性皮膚炎等のアレルギー疾患の原因として広く知られており、有効かつ安全な殺ダニ剤の開発が望まれていた。

発明の開示

本発明者らは、斯かる実情に鑑み鋭意研究を行った結果、イミダゾール又はその誘導体と銀イオンとが結合した化合物が、広範な抗菌抗かびスペクトル及び殺ダニ作用を示すこと、適用される素材に悪影響を与えないこと、更に、毒性、皮膚刺激性、粘膜刺激性が著しく低減されていることを見出し、本発明を完成するに至った。

すなわち本発明は、イミダゾール又はその誘導体と銀イオンとが結合してなる化合物を提供するものである。

また、本発明は、この化合物を有効成分とする抗菌抗かび剤を提供するものである。

また、本発明は、この化合物を有効成分とする殺ダニ剤を提供するものである。

更に、本発明は、この化合物及び担体を含有する抗菌抗かび剤組成物を提供するものである。

更にまた、本発明は、この化合物及び担体を含有する殺ダニ剤組成物を提供するものである。

図面の簡単な説明

図1は実施例1で得られた反応生成物の赤外線スペクトルを示す図面である。
発明を実施するための最良の形態

本発明化合物において、銀イオンと結合しているイミダゾール誘導体としては、イミダゾール骨格を有し、当該イミダゾール骨格中の窒素原子上に置換基を有さないものであれば特に限定されず、2-置換イミダゾール、4-置換イミダゾール、5-置換イミダゾール、2, 4-ジ置換イミダゾール、2, 5-ジ置換イミダゾール、2, 4, 5-トリ置換イミダゾール、2-置換ベンズイミダゾール、4-置換ベンズイミダゾール、5-置換ベンズイミダゾール、6-置換ベンズイミダゾール、7-置換ベンズイミダゾール、2, 5-ジ置換ベンズイミダゾール、

2, 6-ジ置換ベンズイミダゾール等が挙げられる。ここでイミダゾール骨格の窒素原子以外の原子上に置換し得る基としては、アルキル基（好ましくは炭素数1～6）、アルコキシル基（好ましくは炭素数1～6）、 α -アミノカルボキシアルキル基（好ましくは炭素数2～6）等が挙げられる。

より好ましいイミダゾール又はその誘導体としては、イミダゾール、2-アルキルイミダゾール、4-アルキルイミダゾール、5-アルキルイミダゾール、ベンズイミダゾール、2-アルキルベンズイミダゾール、5-アルキルベンズイミダゾール、6-アルキルベンズイミダゾール（ここでアルキル基の炭素数は1～5が好ましい）、ヒスチジン等が挙げられる。

本発明化合物は、イミダゾール又はイミダゾール誘導体の配位子が銀に配位して錯体を形成しているか、又はイミダゾール又はイミダゾール誘導体と銀とが塩を形成していると考えられる。

本発明の化合物は、例えばイミダゾール又はその誘導体と銀イオンとを、得ようとする化合物を製造するのに適切なpH環境下水溶液中で反応させ、生成した沈澱を分離し、水、エタノール等で洗浄することにより得られる。

本発明において使用される銀イオンの供給源としては、水溶性銀塩が好ましく、当該水溶性銀塩としては、例えば、硝酸銀が挙げられる。

本発明化合物は、例えば、銀イオン1モルに対し、イミダゾール又はその誘導体を2モル程度加え、反応せしめることにより得られる。なお、後述の試験例2に示されているように、同一の配位子を用い、しかも配位子と銀イオンのモル比が同じであっても、反応時のpHによって、生成される化合物は異なってくる。このため反応時のpHは、得ようとする化合物に応じて適切に設定する。

かくして得られる本発明化合物は、優れた抗菌抗かび作用及び殺ダニ作用を有するので、そのまま抗菌剤、抗かび剤又は殺ダニ剤として使用できる。また、本発明化合物は、種々の担体とともに配合することにより、抗菌抗かび剤組成物又は殺ダニ剤組成物として使用することもできる。

ここで担体としては、固体担体、液体担体、及びこれらの混合物のいずれも使用できる。

固体担体としては、無機固体担体及び有機固体担体が挙げられ、この無機固体

担体としては例えばシリカ、ヒドロキシアパタイト、ゼオライト、酸化チタン等が挙げられる。これらの無機固体担体と本発明化合物とを含有する組成物においては、この固体担体に本発明化合物が固定化されているのが好ましい。この担体に本発明化合物を固定化せしめるには、例えば加熱処理、化学的結合法等によることが好ましい。

このような無機固体担体及び本発明化合物を含有する本発明組成物は、例えばゼオライトー銀に代表される既存の銀含有抗菌剤の欠点である塩の存在下での銀の置換反応による抗菌活性の低下、銀イオンの光による変色等がない。

また、有機固体担体としては、各種ワックス類及び樹脂類が挙げられる。

また、液体担体としては、水、アルコール類、アセトン等が挙げられる。

本発明組成物における本発明化合物の配合量は特に限定されないが、0.01～90重量%が好ましく、0.01～50重量%がより好ましく、0.01～30重量%が特に好ましい。

本発明の抗菌抗かび剤は広範な抗菌抗かびスペクトルを有し、素材の品質に影響を及ぼさず、かつその効果が長期間にわたり持続するものであり、しかも急性経口毒性、皮膚刺激性、粘膜刺激性等が低いことから下記の種々の素材、例えば繊維、衛生加工品、食品、青果物、クリーンフィルム、包装材料、殺菌性材料、塗料、無機質用グラスフィルター等に適用可能である。

一方、創傷、床ずれなどによる細菌感染予防にも有効であるし、その治療にも応用可能である。現在、抗生物質の多量使用の結果としての抗生物質耐生菌の出現が大きな社会問題となっているが、本発明の抗菌抗かび剤はそのような問題をも一挙に解決するものである。

また、本発明の殺ダニ剤は、タタミ、カーペット、繊維等に使用することにより、殺ダニ効果を長期間奏するので気管支喘息などのアレルギー疾患の予防に有用である。

実施例

以下に本発明を実施例により具体的に説明するが、本発明はこれらに限定されるものではない。

実施例 1

イミダゾール 16.34 g を秤取し、240 ml の水に溶解する。一方、硝酸銀 20.38 g を秤取し、水 60 ml に溶解後、上記イミダゾール水溶液に攪拌しながら徐々に添加する。次に 1 N NaOH で pH 12 に調整する。約 1 時間攪拌を行った後、生成した白色沈澱を遠心分離（9,000 rpm、10 分）により集める。回収された白色沈澱は更に水洗浄（遠心分離条件 9,000 rpm、10 分）を 9 回繰り返し、次いでエタノール、アセトンでそれぞれ 2 回ずつ洗浄（遠心分離条件 9,000 rpm、10 分）を行い、風乾して白色粉末を得る。収量は約 20 g である。

得られた反応生成物の理化学的性質を示す。

（１）各種溶媒に対する溶解性

エタノール、メタノール、クロロホルム、クロロホルム：メタノール（１：１）、アセトン、ジメチルスルホキシド、アセトニトリル、ピリジン、ヘキサン、キシレン、ジエチルエーテル、ジオキサン、ベンゼン及びイソプロピルアルコールには不溶、水には pH 1 以下で溶解。

（２）熱重量分析

熱重量分析法としては、TG-DTG (Thermogravimetry-Derivative Thermogravimetry) を用いた。測定は、島津製作所 TG-30M 型を用い、昇温速度 10 °C/min、測定範囲は室温～500 °C、試料の量は約 10 mg、試料容器は白金製、雰囲気は空气中（50 ml/min）という条件で行った。また、200 °C 以下における重量減少は水分或いは揮発性成分の蒸発とみなし、200 °C 以上での重量減少を熱分解によるものとして、200 °C での重量を 100 % とし、重量減少を測定した。

その結果、1 % 重量減少時の温度は 282 °C、5 % 重量減少時の温度は 306 °C、熱分解速度が最大となる温度（DTG ピーク温度）は 322 °C 及び 425 °C であった。

（３）形状・色

粉末状で白色である。

（４）IR スペクトル

KBr 錠剤法により、HITACHI-270-30 赤外分光光度計で測定し

た。原料のイミダゾールと本物質のスペクトルを図 1 に示す。

イミダゾールのスペクトルに見られる $3300 \sim 2100 \text{ cm}^{-1}$ 付近の N-H の吸収が本物質のスペクトルでは消えており、N-Ag となったと思われる。その他の吸収も、位置、強度ともイミダゾールと本物質とは異なっており、イミダゾールが Ag と塩又は錯体を形成していると思われるが、本物質は水不溶性のため、塩であるか錯体であるかは不明である。

(5) 元素分析

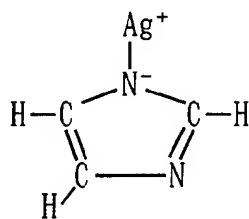
表 1

	C	H	N	O	Na	Ag
実測値	20.6	1.7	15.8	0.3	<0.1	60.7
計算値	20.6	1.7	16.0	—	—	61.7

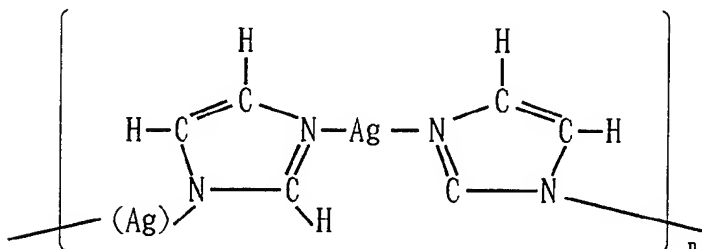
イミダゾールと Ag とが 1 : 1 であるとき、或いは、 $(\text{C}_3\text{H}_3\text{N}_2)_m\text{Ag}_n$ において $m : n = 1 : 1$ であるときに元素分析値は一致する。

以上のデータから本物質の構造は以下の何れかであると推定される。

構造 1



構造 2



実施例 2

イミダゾール誘導体としては、ベンズイミダゾール、2-エチルイミダゾール及びL-ヒスチジンを配位子として銀イオンとの化合物を製造した。

製造は、下記表 2 に示す条件以外は、実施例 1 と同様に行った。製造に用いた原料のモル数、反応時の pH、収量及び反応生成物の色を表 2 に示す。この表にあるように、配位子をベンズイミダゾールとしたときに、反応時の pH を無調整としたものと 12 としたものの 2 種類の化合物を製造した（反応時の配位子と銀イオンとのモル比は同一）。反応生成物は何れも上記各種溶媒に不溶であった。

表 2

配位子名	配位子 (mmol e)	AgNO ₃ (mmol e)	pH	収 量 (g)	色
ベンズイミダゾール	50	25	無調整	6.5	白
ベンズイミダゾール	50	25	12	3.9	白
2-エチルイミダゾール	50	25	12	4.2	白褐色
L-ヒスチジン	80	40	5-6	2.1	白

試験例 1（抗菌活性の測定）

実施例 1 で得られた反応生成物の細菌、酵母及びかびについて最小発育阻止濃度（Minimum Inhibitory Concentration, MIC）による抗菌活性を測定した。測定法は以下の通りである。

細菌：ソイビーン・カゼイン・ダイジェスト（SCD）液体培地 5 ml に接種し、35℃、24 時間前培養し、前培養した菌液の 100 倍希釈液 0.1 ml を 2 ml の検体を含む SCD 液体培地に接種した。35℃、48 時間振盪培養したのち、増殖の有無を判定した。

酵母：グルコース・ペプトン（GP）液体培地 5 ml に接種し、35℃、24 時間前培養し、前培養した菌液の 100 倍希釈液 0.1 ml を 2 ml の検体を含む GP 液体培地に接種した。35℃、48 時間振盪培養したのち、増殖の有無を判定した。

かび：ポテト・デキストロース（PD）又は M40Y 斜面培地に接種した後、

27℃、1週間前培養した胞子を用い、胞子懸濁液（胞子数約 $10^6 / \text{ml}$ ）を調製した。胞子懸濁液 0.1 ml を 2 ml の検体を含む PD 又は M40Y 液体培地に接種した。27℃、1週間振盪培養したのち、増殖の有無を判定した。

抗菌活性測定結果を表 3 に示す。

表 3

供試菌	MIC($\mu\text{g} / \text{ml}$)
<i>E. coli</i>	6.3
<i>B. subtilis</i>	50
<i>S. aureus</i>	50
<i>P. aeruginosa</i>	12.5
<i>C. albicans</i>	50
<i>S. cerevisiae</i>	<3.2
<i>A. niger</i>	50
<i>P. citrinum</i>	6.3
<i>A. terreus</i>	12.5
<i>R. stolonifer</i>	6.3
<i>C. globosum</i>	12.5
<i>C. cladosporioides</i>	12.5
<i>P. islandicum</i>	12.5
<i>A. pullans</i>	25
<i>F. moniliforme</i>	25
<i>E. tonophilum</i>	6.3

試験例 2（抗菌活性の測定）

実施例 2 で得られた化合物を、試験例 1 と同様な測定方法で試験した。測定結果（MIC、単位は $\mu\text{g} / \text{ml}$ ）を表 4 に示す。なおこの表において、配位子名の欄の一段目は、配位子がベンズイミダゾールで反応時の pH は無調整で製造したものの抗菌活性を、二段目は、配位子が同じくベンズイミダゾールで反応時の pH を 12 としたものの抗菌活性を、それぞれ示す。この表が示すように、配位子が同

ー（ベンズイミダゾール）で、しかも反応時の配位子と銀イオンとのモル比が同一（2：1）であっても、反応のpHが無調整のときとpHが12のときとでは、反応生成物の抗菌活性は異なっていた。この結果から、これらの反応生成物は互いに別の化合物であると推定される。

表 4

配位子名	供 試 菌			
	E. coli	B. subtilis	C. albicans	A. niger
ベンズイミダゾール	50	100	25	100
ベンズイミダゾール	25	100	12.5	400
2-エチルイミダゾール	25	100	6.3	200
L-ヒスチジン	25	50	25	50

[MIC($\mu\text{g/ml}$)]

試験例 3（殺ダニ効果）

（試験方法）

ケナガコナダニ培地をとり重量を計測し、培地と同重量の新しい飼料（マウス用粉末飼料）を加えてよく攪拌した。

三角フラスコ 5 個に 3 g ずつ、上記培地を入れ、第 1 の三角フラスコ内培地には 0.3 g の実施例 1 の化合物を加えてよく攪拌した後、飽和食塩水入りデシケーター内に静置した（a とする）。第 2 の三角フラスコ内には 0.03 g の実施例 1 の化合物を加えて同様によく攪拌後、飽和食塩水入りの別のデシケーター内に静置した（b とする）。

第 3 の三角フラスコ内培地はコントロールとして何も加えず、デシケーター内に静置した（c とする）。

各々のデシケーターを室温に 2 週間置いた。その間毎日デシケーターの蓋をあけて内部の空気を入れ替えた。

2 週間後、三角フラスコ内の培地をよく攪拌し、フラスコの壁面に登っているダニも培地内に落して再び攪拌した後、培地 0.1 g 中のダニ生虫数を実体顕微鏡下で計数した。各培地でこの操作を 3 回繰り返し平均値をとった。

(試験結果)

その結果、表 5 に示すように本発明化合物は優れた殺ダニ効果を示した。

表 5 各培地中の生虫数

回数 \ 培地	a	b	c
1	0	105	1456
2	0	95	1028
3	0	84	1054
平均値	0	94.7	1179.3

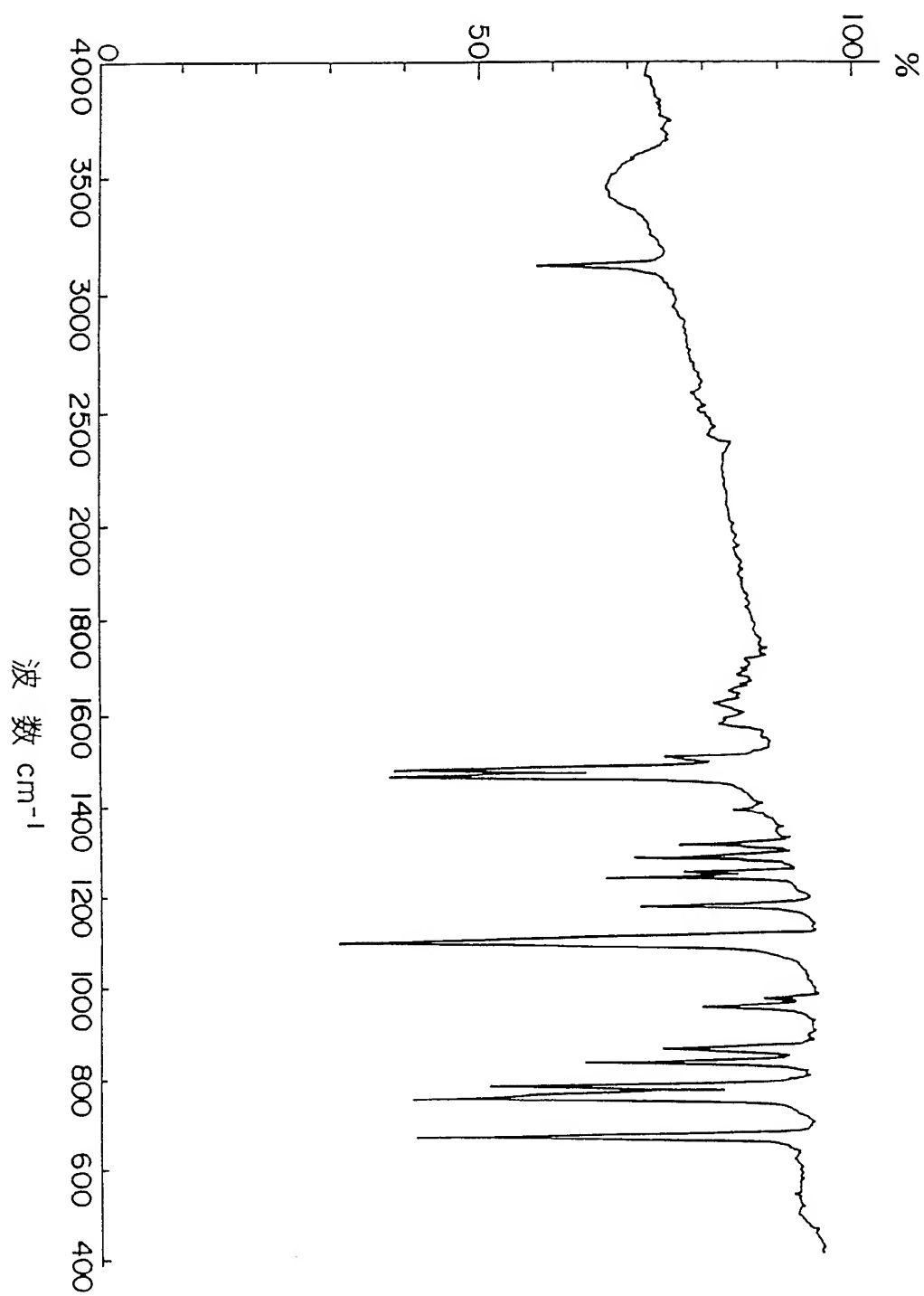
産業上の利用可能性

本発明の抗菌、抗かび、殺ダニ剤は、例えば繊維、衛生加工品、食品、青果物、クリーンフィルム、包装材料、塗料、無機質用ガラスフィルター、カーペット、タタミ等の広い分野の素材に抗菌作用、抗かび作用、殺ダニ作用を付与することができる。

請 求 の 範 囲

1. イミダゾール又はその誘導体と銀イオンとが結合してなる化合物。
2. イミダゾール又はその誘導体が、イミダゾール骨格中の窒素原子以外の原子上にアルキル基、アルコキシル基又は α -アミノカルボキシアルキル基が置換していてもよいイミダゾール又はベンズイミダゾールである請求項1記載の化合物。
3. 請求項1又は2記載の化合物を有効成分とする抗菌抗かび剤。
4. 請求項1又は2記載の化合物を有効成分とする殺ダニ剤。
5. 請求項1又は2記載の化合物及び担体を含有する抗菌抗かび剤組成物。
6. 請求項1又は2記載の化合物及び担体を含有する殺ダニ剤組成物。
7. 担体が、固体担体又は液体担体である請求項5又は6記載の組成物。

図 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/01520

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁶ C07F1/10, A01N43/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁵ C07F1/10, A01N43/50

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, 70:91898 (1969)	1, 2
X	Chemical Abstracts, 113:90238 (1990)	1-3, 5, 7
X	Chemical Abstracts, 103:155707 (1985)	1-3, 5, 7
X	Chemical Abstracts, 76:120979 (1972)	1-3, 5, 7
X	Chemical Abstracts, 75:133670 (1971)	1, 2
E	JP, A, 6-279465 (Tokuyama K.K.), October 4, 1994 (04. 10. 94) & EP, A, 588601	1-3, 5, 7
X	US, A, 4260677 (Minnesota Mining and Manufacturing Company), April 7, 1981 (07. 04. 81), (Family: none)	1, 2

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

December 5, 1994 (05. 12. 94)

Date of mailing of the international search report

December 27, 1994 (27. 12. 94)

Name and mailing address of the ISA/

Japanese Patent Office

Facsimile No.

Authorized officer

Telephone No.

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl.⁸ C07F1/10, A01N43/50

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl.⁸ C07F1/10, A01N43/50

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用了電子データベース (データベースの名称、調査に使用した用語)

CAS ONLINE

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X	Chemical Abstracts, 70:91898 (1969)	1,2
X	Chemical Abstracts, 113:90238 (1990)	1-3, 5, 7
X	Chemical Abstracts, 103:155707 (1985)	1-3, 5, 7
X	Chemical Abstracts, 76:120979 (1972)	1-3, 5, 7
X	Chemical Abstracts, 75:133670 (1971)	1,2

☒ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

「A」 特に関連のある文献ではなく、一般的技術水準を示すもの
 「E」 先行文献ではあるが、国際出願日以後に公表されたもの
 「L」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)
 「O」 口頭による開示、使用、展示等に言及する文献
 「P」 国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献

「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」 同一パテントファミリー文献

国際調査を完了した日

05. 12. 94

国際調査報告の発送日

27. 12. 94

名称及びあて先

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特許庁審査官 (権限のある職員)

脇 村 善 一

4 H 7 4 5 7

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3443

C (続き). 関連すると認められる文献 .

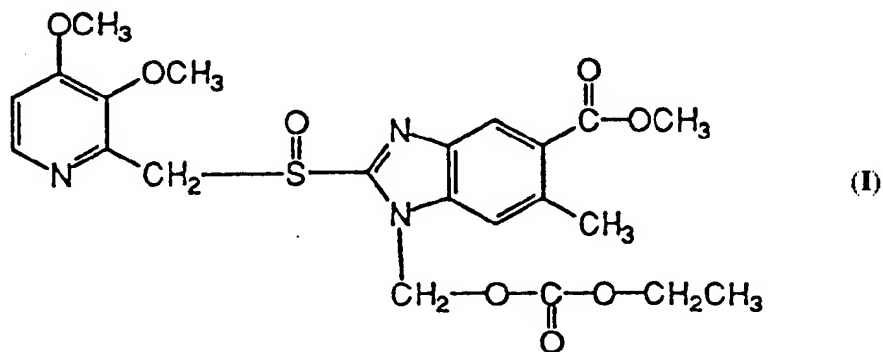
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
E	JP, A, 6-279465 (株式会社 トクヤマ), 4. 10月. 1994 (04. 10. 94) & EP, A, 588601	1-3.5.7
X	US, A, 4260677 (Minnesota Mining and Manufacturing Company) 7. 4月. 1981 (07. 04. 81) (ファミリーなし)	1.2



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(21) International Application Number: PCT/SE94/01093		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).	
(22) International Filing Date: 18 November 1994 (18.11.94)			
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(54) Title: SUBSTITUTED BENZIMIDAZOLE, PROCESSES FOR ITS PREPARATION AND ITS PHARMACEUTICAL USE



(57) Abstract

Novel compounds of formula (I) which inhibit exogenously or endogenously stimulated gastric acid secretion, processes for the preparation thereof and pharmaceutical compositions containing the compounds as active ingredient as well as the use of the compounds in pharmaceutical preparations, and new intermediates obtained.

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**SUBSTITUTED BENZIMIDAZOLE, PROCESSES FOR ITS
PREPARATION AND ITS PHARMACEUTICAL USE
DESCRIPTION**

5 **Field of the invention**

The object of the present invention is to provide novel, stable compounds, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer. Furthermore the novel compounds may be used in the treatment of psoriasis and the treatment of Helicobacter infections.

The invention also relates to the use of the novel compounds in medicine, to pharmaceutical compositions containing said compounds as therapeutic ingredient. In a further aspect, the invention relates to processes for preparation of the new compounds, new intermediates and the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to provide compounds with a good solid state stability and a high level of bioavailability. The compounds of the invention shall also exhibit good stability properties at neutral and acidic pH, a good potency in regard to inhibition of gastric acid secretion and shall not block the uptake of iodine into the thyroid gland.

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Prior art and background of the invention

Different benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned the compound 5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, generic name omeprazole, disclosed in EP 5129, and its single enantiomers. The isomeric mixture of the compounds 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-

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pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate is described in the International Appl. WO 91/19711. The compounds
5 being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). The compounds disclosed in said International Patent Application inhibit exogenously or endogenously stimulated gastric acid secretion and are useful in the prevention and treatment of peptic ulcer.

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It is desirable to obtain compounds with an improved and reproducible stability, especially in the solid state, to further enhance the usefulness of this type of drugs. A high and reproducible stability in the solid state is especially requested for storage purposes. A compound with such a
15 high solid state stability would also be easier to handle (use) in the preparation of pharmaceutical formulations. A high bioavailability, a high potency in inhibiting gastric acid secretion and also a high chemical stability at neutral and acidic pH are still desired.

20 Furthermore, it is desirable to obtain the pure isomeric compound in the form of its single enantiomers with respect to improved pharmacokinetic and metabolic properties of such compounds.

There is no examples given in prior art of the isolated and characterized
25 compounds of the invention.

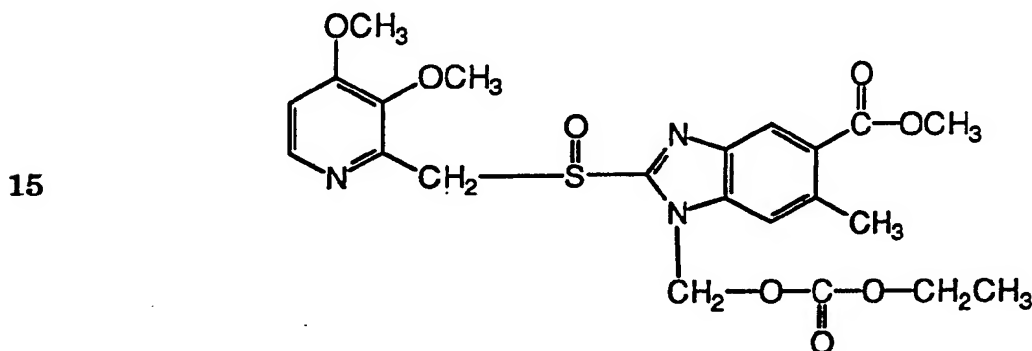
Outline of the invention

The compounds of the invention are effective as inhibitor of gastric acid secretion in mammals including man and do not block the uptake of
30 iodine into the thyroid gland.

It is unexpectedly found that the new compounds, i.e. the pure isomeric

compound or its single enantiomers, show a higher chemical stability in the solid state compared to the isomeric mixture making the compounds especially useful in the preparation of pharmaceutical formulations. It has also been found that the new compounds show high bioavailability and exhibit a high chemical stability also at acidic pH making the compounds useful for non-enteric coated peroral formulations.

The compounds of the invention are 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate and its single enantiomers of the formula Ia and Ib.



Ia (+)-enantiomer

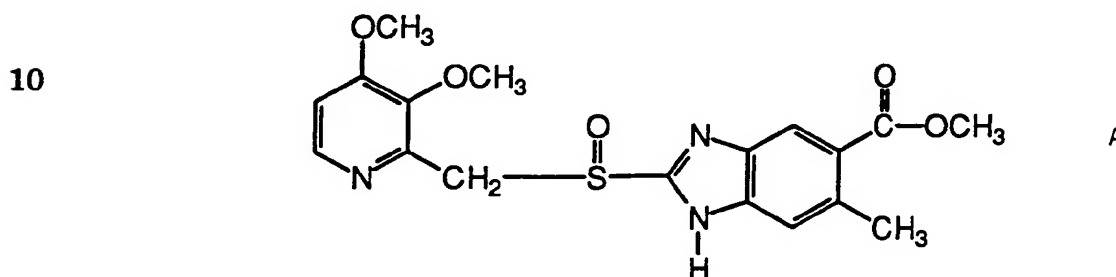
Ib (-)-enantiomer

The compound of the invention has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (two enantiomeric forms). The two pure enantiomeric forms (Ia, Ib), the racemic mixture as well as unequal mixtures of the two are within the scope of the present invention.

The compounds are substantially free from 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate or its single enantiomers. Further, the optically pure (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-

pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate, hereinafter called the (+)-5-isomer, is substantially free from the corresponding (-)-5-isomer and the opposite.

- 5 It is believed that the compounds of the invention are metabolized into the corresponding compounds, carrying H in the N-1 position, (compound A) before exerting its effect.



- 15 The present invention also relates to the use of the compounds of the invention for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and
- 20 gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with
- 25 gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man,
- 30 especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. Furthermore the compounds of the invention may be useful in the treatment of

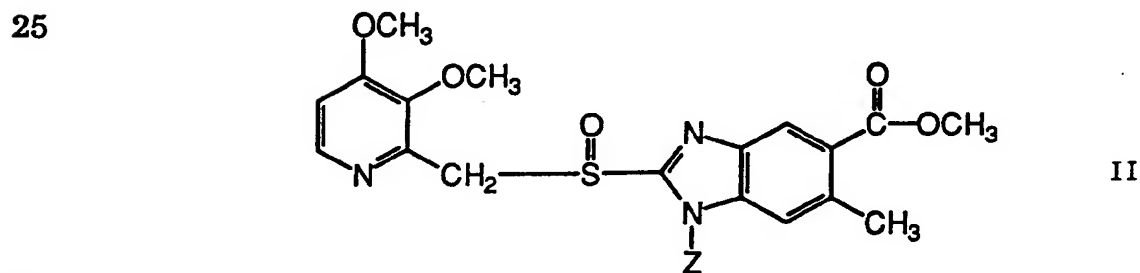
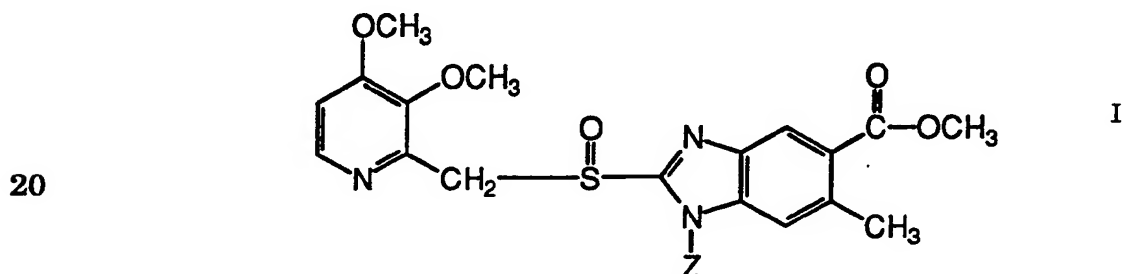
psoriasis as well as in the treatment of *Helicobacter* infections.

The invention also relates to pharmaceutical compositions containing the compounds of the invention, as active ingredient. In a further aspect, the invention relates to processes for preparation of the new compounds, new intermediates and the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

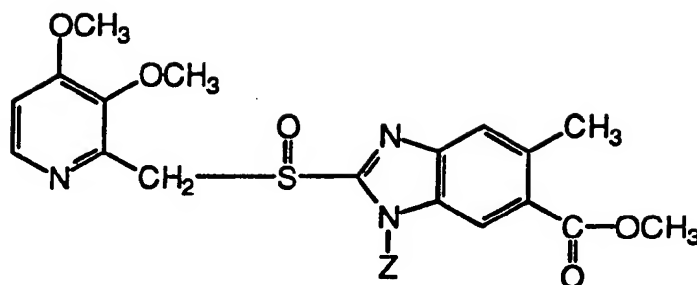
Preparation

The compounds of the invention may be prepared according to one of the following methods a, b or c:

a) Reacting a compound of the formula I or its single enantiomers or an isomeric mixture of the two compounds of the formula II or their single enantiomers



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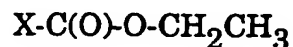
II

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wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate.

- 15 b) Reacting a compound of the formula I or its single enantiomers or an isomeric mixture of two compounds of the formula II or their single enantiomers, wherein Z is hydroxymethyl with a compound of the formula III,

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III

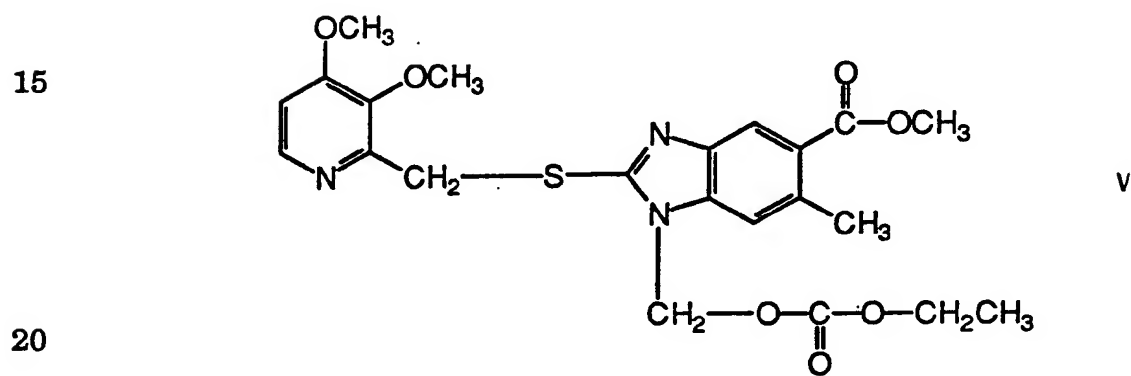
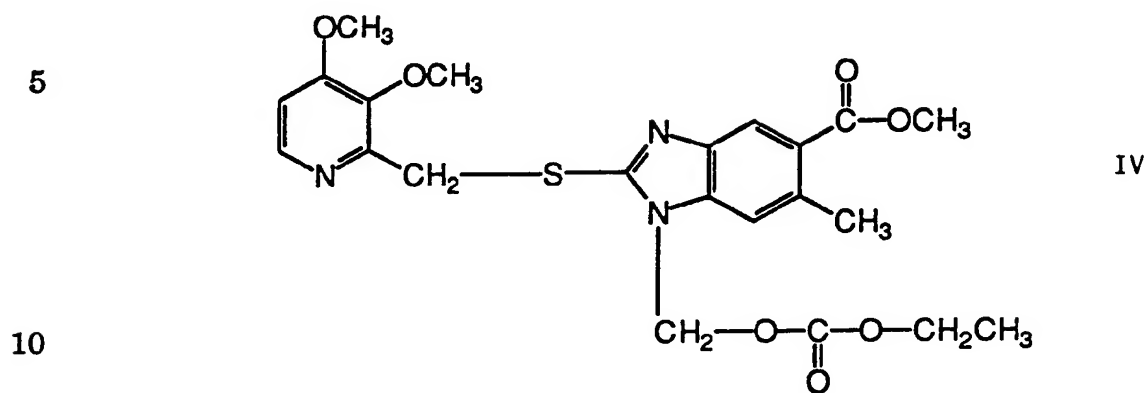
wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

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The reactions according to a) and b) are suitably carried out under protective gas in the absence of water. Suitable solvents are hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or chloroform or acetone, acetonitrile or dimethyl- formamide. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

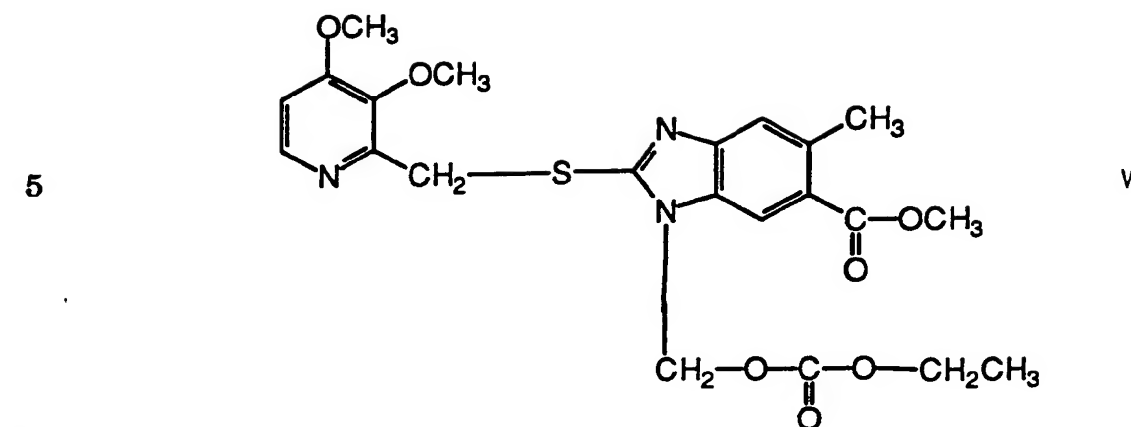
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c) Oxidizing a compound of the formula IV or an isomeric mixture of two compounds of the formula V,



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15 This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, oxone, oxaziridines, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese
20 dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfonyl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

25 The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiologically by using a suitable microorganism.

When mixtures of structural isomers are obtained in any of the above methods, the compound of the invention is isolated by means of crystallization or chromatography.

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The expressions "pure isomeric compound" and "substantially free from" are used with the intention that the compounds of the invention shall

have a purity which is sufficient according to stability, preferably the compounds of the invention should have a purity of more than 90%, preferably more than 97%.

- 5 In some cases the starting materials utilized in the methods a) - c) are unknown. These unknown starting materials may be obtained from known compounds by utilizing processes known per se.

10 Chloromethyl ethyl carbonate may be obtained from ethanol by treatment with chloromethyl chloroformate in the presence of pyridine.

Intermediates of formula I and II, wherein Z is hydroxymethyl are obtained by reaction of the corresponding benzimidazole compounds carrying H in the N-1 position with formaldehyde.

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Starting materials of the formula III may be obtained by known methods, e.g. from ethanol by treatment with phosgene or 1,1'-carbonyl diimidazole or p-nitrophenyl chloroformate.

- 20 Starting materials of formula I and IV can be obtained from the isomeric mixtures of formula II and V by means of crystallization or chromatography.

For clinical use the compound of the invention is formulated into
25 pharmaceutical formulations for oral, rectal, or other modes of administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a
30 further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes.

5 The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g.

10 beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different

15 active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or

25 other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose,

30 sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a dry micro enema, or they may be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents.

Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following example.

Example 1.

Preparation of 5-carbomethoxy-6-methyl-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

2-Phenylsulfonyl-3-(4-nitrophenyl)oxaziridine (707 mg, 2.3 mmol) was

added into a solution of 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate (1.0 g, 2.1 mmol) in methylene chloride (20 ml).

The mixture was stirred at room temperature overnight and evaporated to dryness. Column chromatography (silica gel, EtOAc/hexane) gave the crude compound (800 mg). Re-crystallization from ethanol gave the title compound (97% isomeric purity according to chromatographic analysis and 98% in NMR analysis). Yield 610 mg (59%).

¹H NMR (300MHz)

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1.29 (t,3H), 2.76 (s,3H), 3.89 (s,3H), 3.90 (s,3H), 3.92 (s,3H), 4.24 (q,2H), 4.97 (q,2H), 6.50 (q,2H), 6.78 (d,1H), 7.49 (s,1H), 8.14 (d,1H) and 8.40 (s,1H).

15 **Example 2.**

Preparation of (+)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

20 (+)-5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole 4.6 g (12 mmol) was mixed with potassium carbonate 2.0 g (14 mmol) in acetonitrile (200 ml). Chloromethyl ethyl carbonate 1.8 g (13 mmol) was added together with acetonitrile (100 ml). The resultant mixture was stirred at ambient temperature for 14 h and
25 then the solvent was removed on a rotavapor. The residue was partitioned between water (100 ml) and methylene chloride (200 ml). The organic layer was separated, dried over Na₂SO₄ and then removed to give 5.3 g crude oily residue. The ratio of regioisomers in the crude product was 65:35 in favour of the desired component. Crystallisation
30 from ethyl acetate (50 ml), freshly treated with NH₃(g), afforded 0.66 g of a white solid contaminated with 5% of the undesired regioisomer. The product was dissolved in methylene chloride and the solution was

immediately evaporated. The residue was treated with ethyl acetate (10 ml) to give 0.43 g (7%) of the desired product in the form of a white solid, m.p. 148°-151°C. Chromatographic analysis (chiral AGP) showed that the product consisted of less than 1% of the undesired regioisomer and less than 1% of the undesired stereoisomer. $[\alpha]_D + 130.3^\circ$ (c=1% chloroform).

NMR data are given below.

Example 3.

Preparation of (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

(-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole 0.93 g (2.4 mmol) was mixed with potassium carbonate 0.40 g (2.9 mmol) in acetonitrile (50 ml). Chloromethyl ethyl carbonate 0.37 g (2.6 mmol) was added together with acetonitrile (25 ml). The resultant mixture was stirred at ambient temperature for 14 h and then the solvent was removed on a rotavapor. The residue was partitioned between water (25 ml) and methylene chloride (50 ml). The organic layer was separated, dried over Na_2SO_4 and then removed to give 1.0 g crude oily residue. The ratio of regioisomers in the crude product was 65:35 in favour of the desired component. Crystallisation from ethyl acetate (10 ml), freshly treated with $\text{NH}_3(\text{g})$, afforded 0.21 g of a white solid contaminated with 5% of the undesired regioisomer. The product was dissolved in methylene chloride and the solution was immediately evaporated. The residue was treated with ethyl acetate (5 ml) to give 0.10 g (9%) of the desired product in the form of a white solid, m.p. 148°-151°C. Chromatographic analysis (chiral AGP) showed that the product consisted of less than 1% of the undesired regioisomer and less than 1% of the undesired stereoisomer.

$[\alpha]_D -131.6^\circ$ (c=1%, chloroform).

NMR data are given below.

5	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data δ ppm</u>
2		CDCl_3	1.28 (t, 3H), 2.75 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s,
		300 MHz	3H), 4.23 (q, 2H), 4.88-5.07 (AB-system, 2H), 6.44-6.54
			(AB-system, 2H), 6.78 (d, 1H), 7.48 (s, 1H), 8.13 (d, 1H),
10			8.39 (s, 1H).
3		CDCl_3	1.29 (t, 3H), 2.76 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s,
		300 MHz	3H), 4.23 (q, 2H), 4.89-5.07 (AB-system, 2H), 6.45-6.55
			(AB-system, 2H), 6.78 (d, 1H), 7.49 (s, 1H), 8.14 (d, 1H),
15			8.40 (s, 1H).

Preparation of intermediates

Example A.

20

Preparation of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate

To a suspension of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (8.5 g, 23 mmol) in acetonitrile (100ml) were added K_2CO_3 (6.3 g, 46 mmol) and then chloromethyl ethyl carbonate (3.5 g, 25 mmol). The mixture was stirred overnight. More chloromethyl ethyl carbonate (1.0 g) was added. The mixture was in total stirred for 48 h and then evaporated to dryness. Methylene chloride (300 ml) and water (100 ml) were added to the residue. Methylene chloride layer was separated, dried (MgSO_4) and evaporated. Crude product mixture (10.8 g) was obtained.

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The title compound was purified by re-crystallizations from ethanol. Most of the by-products (6-carbomethoxy-5-methyl-2-[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate and an intermediate compound) were first crystallized out and the majority of the title compound was left in mother-liquor. When the title compound in the mother-liquor was enriched to ca 85% in the mixture, the mother-liquor was evaporated to dryness. The title compound (96% isomeric purity according to NMR analysis) was obtained by a couple of re-crystallizations of the residue from ethanol. Yield 1.35 g (12%).

¹H NMR (300MHz)

1.28 (t,3H), 2.71 (s,3H), 3.91 (s br,9H), 4.21 (q,2H), 4.83 (s,2H), 6.08 (s,2H), 6.78 (d,1H), 7.32 (s,1H), 8.20 (d,1H), and 8.29 (s,1H).

Example B.

Preparation of (+)-5-carbomethoxy-6-methyl-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (1.8 g, 3.3 mmol) was divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used directly in their solutions during the hydrolyses; To the acetonitrile/aqueous

solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl . The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na_2SO_4 . Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173°C. $[\alpha]^{20}_{\text{D}} = +153.1^\circ$ (c=0.5%, chloroform).

Example C.

15 Preparation of (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example B) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH_4Cl . The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na_2SO_4 . Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 270 mg of a yellow oil. The product was crystallized by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 173-

174°C.

$[\alpha]^{20}_D = -150.0^\circ$ (c = 0.5%, chloroform).

Example D.

5 Preparation of 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-(R)-mandeloyloxymethyl]-1H-benzimidazole

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A solution of 0.33 g (8.2 mmol) sodium hydroxide in 1.6 ml water was added to a mixture of 1.4 g (4.1 mmol) tetrabutylammonium hydrogen sulfate and 0.62 g (4.1 mmol) of (R)-(-)-mandelic acid. Chloroform (50 ml) and a mixture of 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl-methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole and 6-carbomethoxy-15 5-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-(chloromethyl)-1H-benzimidazole (as racemates) were added and the mixture was refluxed for 3 hours. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and dried over Na₂SO₄. 20 Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Examples B and C). Yield: 2.4 g, 62%.

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Biological Effects

Bioavailability

Bioavailability, is assessed by calculating the quotient between the areas 30 under blood/plasma concentration (AUC) curve of the compound A following 1) intraduodenal (id) or oral (po) administration of the compound of the invention and 2) intravenous (iv) administration of

compound A, from the rat and the dog. Low, therapeutically relevant doses, were used. Data are provided in Table I.

Potency for inhibition of acid secretion

- 5 The potency for inhibition of acid secretion is measured in the female rat, oral administration and in the dog, oral administration. Potency data are provided in Table I.

Effects on the uptake of iodine into the thyroid gland.

- 10 The effect of the compound of the invention on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland of the compound A, that is the active compound generated in the metabolism of the compound of the invention.

15 Biological tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

- 20 Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen), for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

- Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula, and
- 25 6 ml of Ringer-Glucose is given s.c. Acid secretion is stimulated with infusion during 2.5 h (1.2 ml/h, s.c) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substance or vehicle are given orally 120 min before starting the stimulation, in a volume of 5 ml/kg.
- 30 Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/ L, and acid output is calculated as the product of titrant volume and concentration. Percentage inhibition was calculated from group mean

responses (n=6-10/group) and the ED₅₀-value was obtained from a graphical interpolation on the log dose-response curve. The results are based on acid output during the period 2.5-4.5 hours after dosing.

5 Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. 1-3 days, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substance. The same dose (4 μ mol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.

The area under blood concentration vs time curve, AUC, for the compound A, determined by the linear trapezoidal rule and extra polated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) of the compound A following intraduodenal administration of compounds of the invention of formula I was calculated as

$$F(\%) = \frac{\text{AUC(Compound A)}_{\text{id(Compound A)}}}{\text{AUC(Compound A)}_{\text{iv(Compound A)}}} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability in the Conscious Dog

Harrier dogs of either sex were used. They were equipped with a
5 duodenal fistula for the administration of test compounds or vehicle and
a Heidenhain-pouch for the collection of gastric secretions. Before
secretory tests the animals were fasted for about 18 h but water was
freely allowed. Gastric acid secretion was stimulated by a continuous iv
infusion (12 ml/h) of histamine dihydrochloride at a dose producing
10 approximately 80% of the individual maximal secretory response, and
gastric juice collected in "consecutive" 30-min fractions. The duration of
the histamine infusion was 6.5 hours. The test compound or vehicle were
given orally, iv in a volume of 0.5 ml/kg. The time of administration was
1.5 hours after the start of the histamine infusion. In the case of oral
15 administration, the compound was thus given directly into the acid
secretory main stomach.

The acidity of the gastric juice samples were determined by titration to
pH 7.0, and the acid output determined. Percentage inhibition was
20 individually calculated with reference to acid output in control
experiments with vehicle. These calculations were based on absolute or
fractional rates of acid output. In the latter case, the acid output after
administration of test compound or vehicle was expressed as fractions of
the acid output immediately before the administration. ED₅₀-values
25 were obtained by graphical interpolation of log dose-response curves with
2-3 dose levels and 2-4 dogs. The results are based on secretory
responses 3 hours after dose.

Blood samples for the analysis of test compound concentration in plasma
30 were taken at intervals up to 5 hours after dosing. Plasma was separated
and frozen within 30 min after collection and later analyzed. AUC (area
under the plasma concentration - time curve) from time zero to 5 hours

after dose for compound A, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) of the compound A after oral administration of compounds of the invention was calculated as described above in the rat model.

5

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950; 47:77-81) was followed.

10

Test substance, suspended in 0.5% buffered (pH 9) Methocel, was administered by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300 Bq/kg, 3 ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I -administration, the animals were killed by CO_2 -asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula $100(1-T/P)$, where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered Methocel), respectively. The statistical significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P < 0.05$ was accepted as significant.

25

Chemical stability

The chemical stability of the racemic mixture of the compound of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 2 show the half life ($t_{1/2}$) at pH 7, that is the time period after which half the amount of the original compound remains unchanged and $t_{10\%}$ of pH 2, that is the time period after which 10% of the original compound has

30

decomposed.

The chemical stability in the solid state was tested. The degradation of the compound of the invention was followed by liquid chromatography.

- 5 The substance was stored as a crystalline material at 90°C or at 100°C and analysed after 6 and 14 days or after 2 days. The amount of by-products was evaluated as area per cent of the total peak area. The results are shown in Table 2.

10 Results of biological tests

Table 1 gives a summary of the test data available for the compounds of the invention.

Results of stability tests

- 15 Table 2 gives a summery of the test data available for the compounds of the invention, called "5-isomer", and related compounds disclosed in the prior art. Those related compounds are the isomeric mixture of 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 5-carbomethoxy-6-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate called "isomeric mixture" and 6-carbomethoxy-5-methyl-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, called "6-isomer". In the solid state stability test the amount of degradation products were
- 25 measured after 8 and 14 days storage instead of 6 and 14 days as for the compound of the invention. As can be seen from Table 2 the compound according to the invention is the most stable compound. No degradation products could be detected after 14 days storage at 90°C for the compound of the invention "5-isomer", for the "isomeric mixture" more
- 30 than 20% degradation products are formed during 14 days storage and for the "6-isomer" 20% degradation products are formed already after 8 days storage.

Further, the solid state stability has also been measured at 100°C. At this temperature approximately 20% degradation products are found already after 2 days storage in the "isomeric mixture" and in the "6-isomer". The compound of the invention had only a very slight increase
5 in the amount of by-products during storage at 100°C for 2 days.

Table 1. Biological Test Data

5	Inhibition of acid secretion, oral administration		Bioavailability		Per cent inhibition of ¹²⁵ I-accumulation in the rat thyroid gland after oral administration of 400 µmol/kg
	ED ₅₀	µmol/kg	F %		
	Dog	Rat	Dog (oral)	Rat (id)	
	1.6	3.7	57	75	0

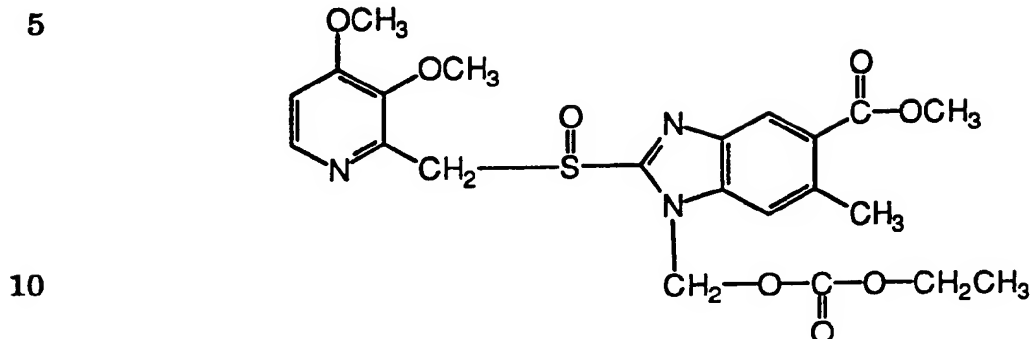
Table 2. Stability Data

Test compound	<u>Chemical stability</u>			<u>Solid stability by products</u>			
	in solution at			as area percent (90°C)			
	pH 7	pH 2		Day 0	Day 6	Day 8	Day 14
	t _{1/2} (h)	t 10% (h)					
5							
10							
25							
	<u>Solid stability by-products</u>			<u>Solid stability by-products</u>			
	as area percent (100°C)			as area percent (100°C)			
	Day 0	Day 2		Day 0	Day 2		
15							

The invention: "5-isomer"
 Ref. "isomeric mixture"
 Ref. "6-isomer"

CLAIMS:

1. A compound having the formula



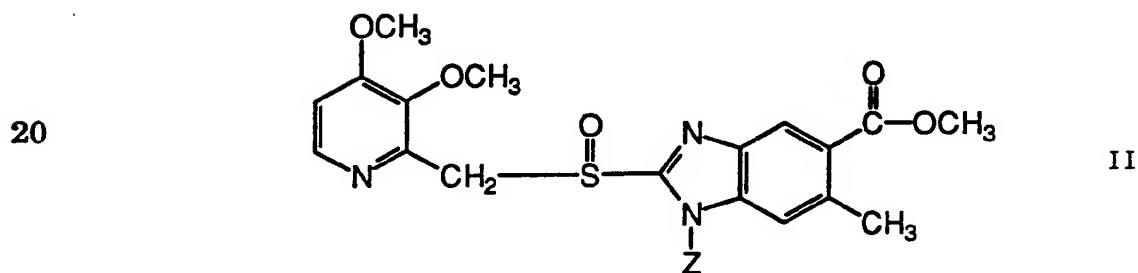
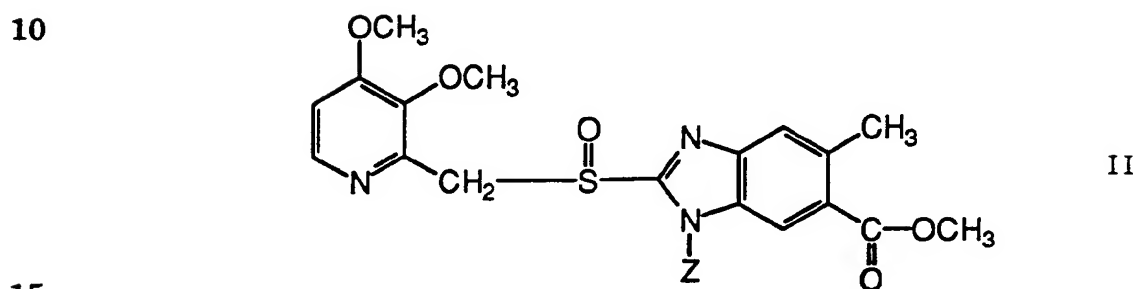
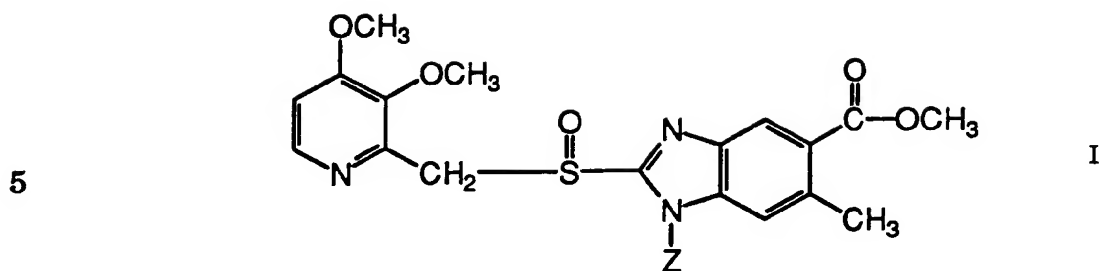
2. 5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free from 6-carbomethoxy-5-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

3. (+)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

4. (-)-5-carbomethoxy-6-methyl-2-(((3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole-1-ylmethyl ethyl carbonate.

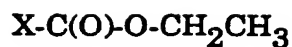
5. A process for the preparation of a compound according to claim 1 characterized by

a) reacting a compound of the formula I or its single enantiomers or an isomeric mixture of two compounds of the formula II or their single enantiomers,



25 wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate,

b) reacting a compound of the formula I or its single enantiomers or an
 30 isomeric mixture of two compounds of the formula II or their single enantiomers, wherein Z is hydroxymethyl with a compound of the formula III,



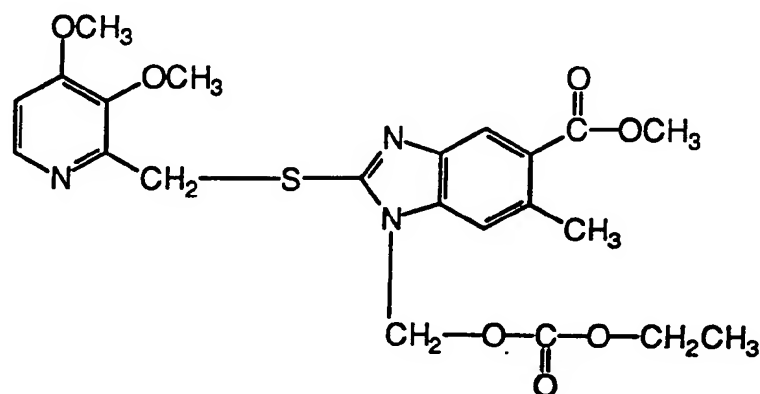
III

wherein X is Cl or imidazole or p-nitrophenoxy or a functionally
equivalent group, in the presence of a suitable base such as
5 triethylamine, or

c) oxidizing a compound of the formula IV or an isomeric mixture of two
compounds of the formula V,

10

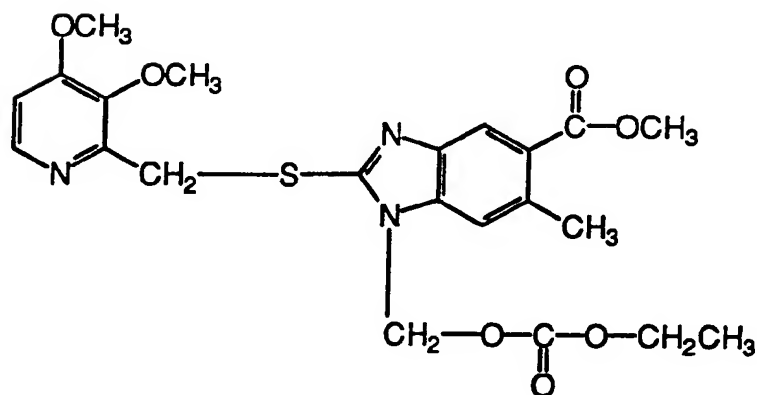
15



IV

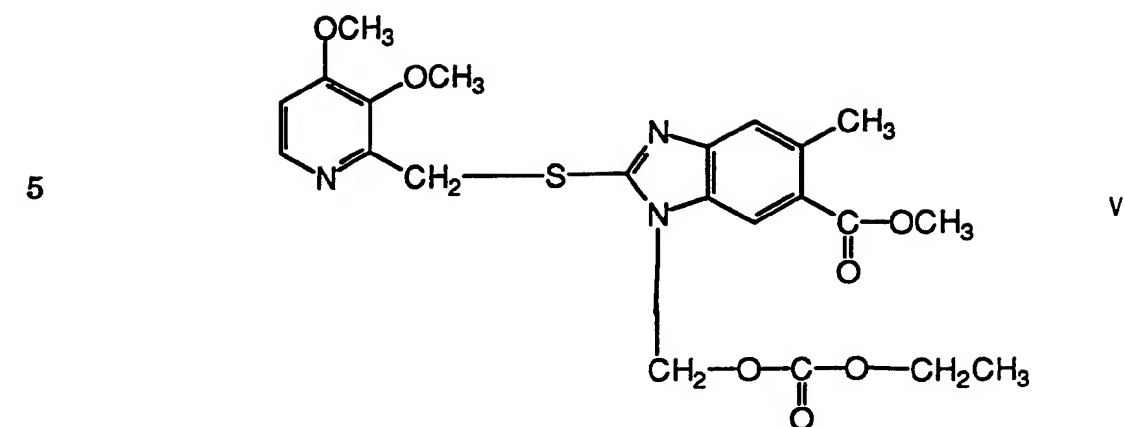
20

25



V

30



and when mixtures of structural isomers are obtained in any of the above methods the pure isomeric compound is isolated by crystallisation or chromatography.

6. A process according to claim 3, wherein the reactions according to a) and b) are carried out under protective gas and in the absence of water, and the oxidation according to c) is carried out in a solvent by using an oxidizing agent.

7. A compound according to claim 1 for use in therapy.

8. A pharmaceutical composition containing the compound according to claim 1 as an active ingredient.

9. A method for inhibiting gastric acid secretion by administration to

mammals including man in need of such treatment an effective amount of the compound according to claim 1.

5 10. A method for treatment of gastrointestinal inflammatory diseases comprising administration to mammals including man in need of such treatment an effective amount of the compound according to claim 1.

10 11. Use of the compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.

12. Use of the compound according to claim 1 in the manufacture of a medicament for treatment of gastrointestinal inflammatory diseases in mammals including man.

15

13. The compound 5-carbomethoxy-6-methyl-2[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/01093

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 9119711 (AKTIEBOLAGET ASTRA), 26 December 1991 (26.12.91), see example 1 -----	1-8, 11-13

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

17 February 1995

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

31/12/94

International application No.

PCT/SE 94/01093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9119711	26/12/91	AU-B- 649453	26/05/94
		AU-B- 649456	26/05/94
		AU-A- 8009791	07/01/92
		AU-A- 8061791	07/01/92
		CA-A- 2083606	21/12/91
		CA-A- 2083714	21/12/91
		CN-A- 1058212	29/01/92
		CN-A- 1058213	29/01/92
		EP-A- 0535081	07/04/93
		EP-A- 0593463	27/04/94
		HU-D- 9204033	00/00/00
		HU-D- 9204034	00/00/00
		NZ-A- 238546	25/03/94
		OA-A- 9682	15/05/93
		OA-A- 9683	15/05/93
		WO-A- 9119712	26/12/91



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP95/00650 (22) International Filing Date: 23 February 1995 (23.02.95) (30) Priority Data: P 44 06 641.4 1 March 1994 (01.03.94) DE 873/94-6 23 March 1994 (23.03.94) CH 94203112.1 26 October 1994 (26.10.94) EP (34) Countries for which the regional or international application was filed: AT et al. (71)(72) Applicant and Inventor: GERGELY, Gerhard [AT/AT]; Gartengasse 8, A-1053 Wien (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): GERGELY, Thomas [AT/AT]; Gartengasse 8, A-1053 Wien (AT). GERGELY, Irmgard [AT/AT]; Gartengasse 8, A-1053 Wien (AT). GERGELY, Stefan [AT/AT]; Gartengasse 8, A-1053 Wien (AT). (74) Agent: PATENTBÜRO DR. BÜCHEL; Letzanaweg 25, FL-9495 Triesen (LI).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: GRANULAR PRODUCT OR TABLET CONTAINING AN EFFERVESCENT SYSTEM AND AN ACTIVE PHARMACEUTICAL SUBSTANCE, AS WELL AS A METHOD FOR ITS PREPARATION (57) Abstract <p>In accordance with this invention, there is provided a granular product with an effervescent system which comprises acid-sensitive pharmaceutically active substances, such as, for example, beta-carotene, cimetidine, ranitidine or cisapride, which is specially useful to prevent antacid action, having an acid-binding capacity below about 5meq, at a weight of about 1.6 to about 2.3 grams. The effervescent grains are made from carrier crystals of at least one solid, edible organic acid, preferably citric acid, and are present as a granular product, separate from the pharmaceutically active substance, and are coated with at least one layer of a neutral substance which is soluble in water and/or alcohol and which is able to bring about a melting point depression of the acid grains at their surface, such as, for example, a water-soluble polymer, a higher alcohol, a carbohydrate and/or a hydrocolloid. A second coating contains at least a part of the alkali and/or alkaline earth carbonate or bicarbonate provided for the total dosage.</p>		

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Granular product or tablet containing an effervescent system and an active pharmaceutical substance, as well as a method for its preparation

5 Field of the Invention

This invention relates to a granular pharmaceutical preparation or more particularly a tablet containing an effervescent system and a - preferably acid-sensitive -
10 pharmaceutical substance, such as cisapride, beta-carotene, an H₂ blocker such as cimetidine or ranitidine, and/or a substance which is to be administered in an effervescent pharmaceutical preparation with comparatively small amounts of effervescent components or a comparatively low acid-
15 binding capacity.

Background of the Invention

Heretofore it has been possible only with difficulty to
20 incorporate acid-sensitive drugs in stable form into effervescent tablets or effervescent instant granular products, since in contact with the acid of the effervescent system such compositions hydrolyze or decompose, i.e. they are not shelf-stable. Furthermore, whenever such a substance
25 also affects the surface tension of water, frothing occurs which is highly undesirable for the consumption of the effervescent solution, or in any event, hydrophobic particles of the drug tend to creep upward on the glass. On the other hand, in certain cases, the antacid side-effect of
30 an effervescent tablet is undesirable for many drugs. Therefore an object of this invention is to provide an effervescent system which will avoid the aforesaid disadvantages and offer the possibility of administering to a patient pharmaceutical substances, inclusive of acid-
35 sensitive substances which have hydrophobic properties or properties influencing the surface tension of water, in pleasant-to-drink effervescent solutions. It is a further object of this invention to create an effervescent tablet or

- 2 -

an instant effervescent granular product with an acid binding capacity of less than 5 meq, in order to avoid undesired antacid effects. This is especially advantageous for all H₂ blockers. Lastly, it is desired that the tablet or granular product is to dissolve rapidly in water at a temperature of about 15-20°C in less than about 2 minutes.

Summary of the Invention

10 The solution to the aforesaid problems can be achieved in a surprisingly simple, cost-effective and efficient manner in accordance with this invention e.g. by first substantially coating acid particles with a composition comprising at least one neutral substance which causes a depression of the
15 melting point of the acid grains at their surface, and thereafter anchoring thereon at least one second coating which contains an alkali and/or alkaline earth carbonate and/or bicarbonate, and optionally a partial reaction product of the carbonate or bicarbonate with the same or a
20 different organic acid.

The invention is more fully discussed in detail below along with a detailed discussion and illustration of several preferred embodiments.

25

Detailed Description

Neutral substances within the meaning of this invention include polymers soluble in water and/or alcohol, such as
30 e.g. polyvinylpyrrolidone, carbohydrates, such as saccharose, pentaerythritol, glucose, and fructose (although the latter two, under the influence of the only slightly alkaline effervescent-grain surface due to the bicarbonate coating, are subject to a Maillard reaction tending to make
35 them yellow and therefore they are not particularly preferred herein), hydrocolloids, such as maltodextrin, dextrin and

- 3 -

the like; especially preferred are higher alcohols, such as xylitol, mannitol and sorbitol.

Various embodiments of the invention are described in the
5 defining clauses of the dependent claims.

It is true that W093/00886 discloses that a foreign acid, possibly gluconic acid delta-lactone, which hydrolyzes to gluconic acid, can be incorporated at the surface of acid
10 vehicle crystals, with the result that the crystal lattice is disturbed and a melting point depression is achieved. However, such a measure cannot of course provide adequate protection for acid-sensitive active substances. It has therefore also been impossible hitherto to use the invention
15 of W093/00886 for acid-sensitive active substances in practice.

It has also been proposed (British Patent 1,270,781) to coat acid vehicle crystals for effervescent tablets with a thin
20 polymer layer, such as, for example, with polyvinylpyrrolidone, carboxymethylcellulose or the like. However, this results in an undesirable retardation of the dissolution time and, in the case of the 1 to 5% by weight of polyvinylpyrrolidone described there in the Examples,
25 foam formation problems; furthermore, some acid is always transferred from the vehicle crystal to the layer in solution when the coating is applied by means of ethanolic or aqueous solution, whereby the acid-sensitive active substances would not be protected sufficiently. In addition,
30 however, those skilled in the art have for over 20 years been unable satisfactorily to solve the problem of accommodating acid-sensitive active substances in effervescent systems not only in a shelf-stable manner but also in relatively small tablet weights with very low acid
35 binding capacity and short dissolution time. An effervescent tablet is generally defined as being particularly rapid when the dissolution (or complete

- 4 -

suspending) of the tablet components takes less than 120 sec, preferably 90 sec or less.

According to the invention, however, after (preferably only a small amount of) the neutral substance has been applied to the acid grains, alkali and/or earth alkaline carbonate and/or bicarbonate particles are anchored on the grain surface in order to prohibit an interaction between the acid and the active substance.

10

Furthermore, the process proposed in EP-A1-415 326 for coating acid vehicle crystals with several times the amount of sugar in order, in combination with bicarbonate, to achieve a slightly prickling effect, for a chewable tablet or lozenge has not been able to solve the combination of the problems or tasks: such a system would not be sufficiently reactive to dissolve an effervescent tablet in water within a reasonable time. It was the aim of the said EP-A1 to slow down the reaction between acid and carbonate in order not to produce an undesired high effervescent effect in the mouth.

20

If, as disclosed in the prior art (US-A-4 127 645), a tablet having a core of acid, bicarbonate and calcium were coated with a neutral substance, for example with sorbitol in an aqueous, alcoholic or in a water/alcohol-solution, such a tablet would not provide reliable protection for acid-sensitive active substances contained in the core. However, if the mixture were pressed with a neutral substance (e.g. maltodextrin, if necessary as a mixture with sugar, US-A-4 650 669; sorbitol with vitamins, US-A-5 223 264, only suitable as a prickling chewable tablet) to give tablets, then either both reactants would be coated together or undesirable agglomerated granules would occur. In both cases, the reaction on dissolution of the tablet would take place too slowly and the dissolution time would thus be undesirably increased, or the solution would contain undesirably large amounts of sugar. Furthermore, it is very

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- 5 -

probable that, in agglomerated granules, acid particles too would be present unprotected at the surface of the granules; however, this results in greater instability for acid-sensitive active substances.

5

In U.S. Patent No. 4,867,942, a method is described in which vehicle crystals of a solid, edible organic acid are covered on their surface with a pre-reacted solution serving as buffer, particularly an acid alkali and/or alkaline earth salt of a solid, edible organic acid. Thereafter, more of the acid crystals and amounts of carbonate or bicarbonate are anchored side by side on this coating. Water which is released in the various neutralization partial reactions is removed by a final treatment with alcohol and vacuum drying. Such a process is disadvantageous, however, in that, for acid-sensitive drugs, on the acid crystal surface an additional acid simultaneously enters into a reaction with the alkali carbonate, and the reaction thus proceeds too fast and consequently not sufficiently uniformly. Therefore, the product that forms from this method cannot completely prevent the reaction of an acid-sensitive drug mixed in with it, due to the acid crystals lying on the surface of the granules.

25 In contrast, the structure of the effervescent system according to this invention not only prevents direct contact of an acid-sensitive drug with the acid crystals thereby providing an effervescent tablet or granular product with substantially more shelf-stability, but it also permits the preparation of substantially smaller tablets, i.e., those with smaller amounts of effervescent components which, when dissolved, result in a buffer system. Thus, the present tablets according to the invention, in contrast to buffer systems of antacid effervescent preparations, can remain at far less than 5 meq of acid binding capacity. Also, in terms of product preparation, a retarded reaction and better compressibility into tablets is obtained. With the aid of

- 6 -

this invention, an effervescent tablet can be prepared which for the first time contains an acid-sensitive drug, such as cisapride, or an H₂ blocker such as cimetidine, and which has an acid-binding capacity of less than 5 meq for a tablet
5 (or granular product) weight of only 1.6 to 2.3 g.

Further, in accordance with an especially advantageous embodiment of this invention, after the acid crystals have been covered with a coating of neutral substance, at least a
10 portion of the carbonate and/or bicarbonate particles intended for a full dose can be applied to this coating, so that effervescent grains are formed from acid crystals on which a first coating of neutral substance has formed, and thereon a second coating of carbonate and/or bicarbonate,
15 which has partially reacted with the acid in some cases.

The invention can be particularly expediently used for products or processes as described, for example, in EP-B1-76 340, US-A-4 867 942 and WO93/00886, and whose description
20 and claims are herein regarded as having been disclosed.

The application of the neutral substance, especially a sorbitol solution, for example, causes a depression of the melting point on the surface of the citric acid crystals.
25 Thus, on the one hand, the adhesive force for the next coating containing alkali or alkaline earth carbonates and/or bicarbonates increases, and at the same time this signifies a slower and therefore more uniform reaction of the citric acid crystal surface and better passivation, so
30 that the acid-sensitive drugs are less attacked by the effervescent grains. On the other hand, the melting point depression protracts the recrystallization time of the citric acid or of the citrates that have formed, which signifies better compressibility of the effervescent
35 granules over a longer period of time.

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The amount of neutral substance applied to the acid vehicle crystals depends on the amount of solvent with which the acid can be wet, since a maximum of 50 - 70 % by weight can be dissolved in an aqueous solution. It is therefore

5 preferably added in an amount of 0.05 bis 1.0, in particular 0.07 bis 0.8, % by weight, based on the acid. Additions of less than 0.07 have only a weak effect and those of less than 0.05 have no effect which is relevant according to the invention: the shelf-stability of acid-sensitive active

10 substances is reduced. Additions of over 0.8 generally begin to have an interfering effect, and at above 1.0 the reactivity of citric acid and of the effervecent system is considerably slowed down.

15 However, this may be less troublesome in the case of granules since a longer dissolution time tends to be desirable there in order to allow the granules to sink on introduction into water and only thereafter to undergo a reaction for dissolution. Otherwise, however, the amounts of

20 neutral substance which can be applied to, for example, citric acid are determined by the amount of solution with which the citric acid can be wet, since the neutral substances are in fact applied in solution, and a 50 to max. 70% solution can be prepared. The citric acid crystals

25 cannot be wet with an infinitely large amount of water and hence solvent.

In certain circumstances, the neutral coating, especially if carbonate and/or bicarbonate particles are anchored on it,

30 can also contain small amounts of a solid, edible organic acid, and in some cases an acid different from the one of which the vehicle crystals consist - as disclosed per se in another context - but here also in order to intensify the melting point depression and/or to control the effervescent

35 reaction and rate of dissolution.

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Each such effervescent grain is, taken by itself, actually a small effervescent "tablet", and effervesces by itself. Therefore, if desired, a short dissolving time, small quantity and low acid-binding capacity can be achieved.

5

Experiments thus far towards achieving a fast-acting, small effervescent tablet by the use of monosodium citrate instead of citric acid have failed, because this greatly slows the effervescent reaction, since the monosodium citrate reacts
10 more slowly with sodium bicarbonate, and such tablets usually have an acid consuming capacity exceeding 5 mEq.

On the other hand, a very thin monosodium citrate coating in accordance with this invention, especially as a third or
15 fourth layer, which can contain an additional neutral substance if desired, acts advantageously because 1 mol of monosodium citrate binds 1 mol of water of crystallization and thus contributes to the drying or to maintenance of dryness. Furthermore, in any case, uncovered citric acid
20 surfaces can be covered again or more completely with bicarbonate.

Additionally, since many substances exhibit some form of taste sensation of which many are unpleasant, especially
25 those exhibiting bitterness, it is desirable to keep the final effervescent solution, especially since it is in beverage form, within the pH range of 3.8 to 4.6. Experience has shown that within this range particularly bitter substances can be more effectively masked.

30

While not obligatory, it is preferable to remove residual water from the reaction granules in the course of their preparation by a final treatment with alcohol. Alcohol may disrupt the bonding of water of crystallization, because
35 during drying the residual moisture is removed along with the alcohol by evaporation. Small amounts of an antifoaming

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agent can also be added to the alcohol in order to accelerate the dissolution of the final tablet.

Many of the aforementioned drugs, especially cimetidine and
5 cisapride, often cause frothing in an effervescent tablet.
This is not due, however, to foaming such as that caused by
tensides. That is to say, the active agents themselves, when
stirred into water, do not foam. Instead, when the
effervescent particles in the tablet dissolve, bubbles of
10 carbon dioxide form.

These bubbles burst and leave the CO₂ on the surface. Now,
if a less soluble or more hydrophobic substance is present,
the undissolved particles envelop the CO₂ bubbles, and by
15 forming such a film successfully prevent rapid bubble
bursting, so that the bubbles with this film on the surface
collect and thus a "foam" is formed. However, the "foam"
already forming between the effervescent grains interferes
with the continued reaction, and thus with the rapid
20 dissolution of the tablet or granules. This circumstance is
combated according to the invention by the addition of very
small amounts of at least one antifoaming agent with the
result that any "foam" that forms as the effervescent
reaction begins immediately collapses.

25 The antifoaming agent is preferably added in an amount of
0.005 bis 0.5% by weight, based on the total amount
including any fillers, flavors, etc., or 0.05 - 2.0% by
weight, based on active substance. Additions of less than
30 0.005 have no effect relevant according to the invention;
additions of more than 0.5 give rise to troublesome or
unacceptable side effects.

In the case of active substances which are soluble, although
35 not too freely soluble, as in the case of cimetidine, a
percentage of dimethicone of 0.1 - 0.3% by weight, based on
active substance, is used, which is equivalent to the use of

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0.016 - 0.028 percent (about 0.03%) based on the total tablet weight. The situation is somewhat different in the case of an insoluble hydrophobic active substance, such as cisapride (the monohydrate is used), where 1% of simethicone
5 is used, based on the active substance, but an amount of 0.006% results when based on the tablet weight of 1.6 g. It is evident that the cisapride, as a slightly soluble, hydrophobic active substance, requires a larger amount of antifoaming agent for suppressing the foam, but the required
10 fillers and the effervescent base result in a substantially smaller amount of simethicone being used per tablet, so that the ratios are inverted.

In the case of the soluble active substances, such as
15 cimetidine and ranitidine, the simethicone is required in smaller amounts, in order to suppress the smaller tendency to foaming in the local reaction on dissolution of the effervescent tablet, whereas in the case of cisapride - as already mentioned - the tendency to foam is substantially
20 greater and the principle is therefore also slightly different.

If larger amounts are used, film formation of simethicone occurs at the surface after dissolution of the effervescent
25 tablet, by virtue of the fact that - especially in the case of insoluble active substances - particles of the active substance collect and remain hanging and thus result in unattractive dissolution behavior, this film then additionally having the tendency to form a ring on the glass
30 wall.

In some cases, however, very small amounts of a tenside, for example, docusate sodium, are also added. Due to their wettable nature, such drug particles dissolve more quickly
35 and no longer adhere to the foam bubbles. The proportion of such substances must be determined very precisely to achieve the desired dissolving characteristics.

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Although in some cases the antifoaming agent can be applied to the effervescent system and/or to the drug, this is not preferred according to the invention. In the first case, it might cause undesirable slowing of the dissolution and reaction of the effervescent components unless very slight amounts of antifoaming agent sufficient for the achievement of the desired effect are used. In the second case, only those drugs are involved which, when the antifoaming agent is drawn onto them from a solution in a solvent (e.g., methyl ethyl ketone and acetone) at 40°C, do not lose any of their solubility or stability. Additionally, in the course of production with the use of finely powdered drugs the addition of antifoaming agents may lead to poor distribution because of drug particles attaching themselves to the antifoaming agent droplets.

It is therefore preferred, in accordance with this invention, that first the formation of a typical granular product from antifoaming agents and a neutral substance is undertaken, which product is thereafter mixed with the effervescent system and the drug, plus additional adjuvants if desired (e.g., perfumes, sweeteners and the like) and the mixture then compressed into tablet form.

The moisture released in the preparation of the effervescent system by the neutralization reaction, and not entirely removed by heating and/or vacuum treatment, as well as moisture picked up from the air during storage, can best be bound by the addition of a moisture-binding agent, especially anhydrous sodium carbonate (which can absorb 10 mols of water per mol) or sodium sulfate. The agent can be bound either by applying it to one or more of the coatings applied to the vehicle crystals, or by adding it to the total mixture. This improves shelf life because the reaction of the acid-sensitive active agent with the acid is further suppressed or completely prevented by the reduction of

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moisture. However, excessive amounts of such moisture-binding agent, for example sodium carbonate, are not desirable as it may retard the effervescent reaction.

- 5 Sodium carbonate as a drying agent, therefore, should not be used for completely covering the effervescent grains, since it is preferable to operate with only small quantities effective to merely dry the residual moisture, or to retard the reaction during manufacture, and to avoid undesirably
- 10 lengthening the dissolving time of the tablet. Therefore, the final addition of sodium carbonate should not be used for complete coverage (or a tablet coating), due to both the quantity and the grain size (approx. 0.1 - 0.05 mm), and it is therefore not suitable for producing a continuous coating
- 15 on the bicarbonate already present. However, it can be partially hooked onto the effervescent grains. It is also possible, however, not to add the sodium carbonate until after the drying operation.
- 20 In principle, the percentage amount of sodium carbonate per tablet depends on several factors, such as, for example, the amount of effervescent base used, the amount and type of the fillers used, the presence of other carbonates, such as, for example, calcium carbonate, etc.
- 25
- The moisture-binding agent, in particular sodium carbonate, is preferably added in an amount of between 1 and 10, in particular 4 - 6, % by weight (based on the total amount, including any fillers, flavors, etc.). Additions of less
- 30 than 4 have only a weak effect, and with those of less than 1, the drying effect and increase in stability is too small, they have no effect relevant according to the invention. Additions of over 6 generally begin to have a troublesome effect because sodium carbonate dissolves more slowly and
- 35 reacts more poorly; above 10% the dissolution time is already significantly lengthened, since sodium carbonate first absorbs water (up to 10 molecules of water of

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crystallization) on dissolution of the effervescent tablet, i.e. is calcined and only then reacted with the citric acid.

- Here it is to be emphasized that 1 mol of water of
- 5 crystallization can be bound per mol by sodium citrate alone developing in or on the sorbitol layer, and in spite of any residual moisture present the sorbitol layer prevents or hinders any acid harm to the drug.
- 10 If all of the prescribed steps are followed in accordance with the invention, effervescent tablets can be produced, even with the difficult substances referred to, which at a tablet weight of, e.g., 1.6 g, will attain a dissolving time of less than 100 seconds. It is also to be noted that
- 15 especially cimetidine, due to its hydrophobic character, further lengthens the dissolving time in comparison with other drugs, under otherwise equal conditions.

- Granulation with sorbitol solution permits rapid dissolution
- 20 without the incorporation of an extraneous acid that is otherwise necessary, for example, according to WO93/00886.

- Furthermore, during the preparation of the effervescent systems of this invention, and in any case of the tablets
- 25 themselves, the steps taken according to the invention will enable the control of reactions which take place at the surface of individual crystals or granules, which thus constitutes a local mechanism, while also during dissolution the above-described desired advantages will be achieved
- 30 throughout.

- The system is also extraordinarily well suited for the processing of substances which are both acid-sensitive and sparingly soluble in water. Such substances, such as
- 35 cisapride for example, exhibit very unpleasant behavior in suspension, since, as mentioned above, they tend to froth together with the effervescent system, adhere to a glass

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wall, form unpleasant rings and tend to agglomerate on the surface of the drink.

All the aforesaid problems can be effectively combatted by preparing separate granules. For this purpose in yet another embodiment of this invention, there is provided a vehicle which can consist of an Aerosil and/or a neutral substance, on which the drug is applied preferably with the surface of its grains partially dissolved, and/or with binding agents and/or tensides if desired, and dried, or is bound to the vehicle surface by means of binders.

The amount of the suspended substance is limited to at most 8, preferably at most 4.5, % by weight (based on the total mixture), for example for cisapride, since larger amounts would result in increased sinking of the granule particles after dissolution of the tablet. On the other hand, the amount of binder used is likewise limited to 1% by weight, since it otherwise leads to undesirable agglomerated granules of active substance, suspended substance and binder, which dissolve only with difficulty and then sink to the bottom, i.e. prevent the desired suspension.

The invention will now be more fully described and understood with reference to the following examples of preferred embodiments. It is to be understood, however, that these examples are for illustrative purposes only, and many other embodiments and variations will be readily apparent to those persons skilled in the relevant art and are not intended to limit the scope of this invention or the claims or the spirit thereof in any way.

Alternatively, the drug can also be dissolved in the methyl ethyl ketone or in acetone and coated onto mannitol, Aerosil^(R) and sodium bicarbonate.

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Example 1: Preparation of effervescent tablets
containing 200 mg of cimetidine

a) Preparation of the effervescent system

5 102 parts by weight of coarse citric acid and 25 parts by weight of finely powdered citric acid (the latter is preferable for improving build-up to effervescent grains on the vehicle crystal as the powder particles provide a rough surface on which up to about 30% of bicarbonate can be
10 anchored) or tartaric acid are aspirated into a preheated vacuum tank and heated to approx. 60°C with stirring. Next, 0.85 parts by weight of a solution 1, which has been formed from 36 parts by weight each of water and sorbitol, 21 parts by weight of citric acid and 7 parts by weight of sodium
15 bicarbonate, is aspirated and distributed on the citric acid by mixing. Thereafter, 52.5 parts by weight of sodium bicarbonate and 4.4 parts by weight of aspartame are added to this mixture, which is then stirred and dried by a vacuum of up to 200 mbar, after which 1.9 parts by weight of sodium
20 carbonate are aspirated and distributed in the mixture by stirring, and the mixture is then dried by a vacuum of up to 15 mbar.

Next, a further 0.6 parts by weight of said solution are
25 aspirated and distributed in the mixture by mixing. The resultant effervescent grains are dried in a vacuum of up to 20 mbar with stirring. If necessary, 0.25 parts by weight of 96% ethanol are also employed to dry the mixture, and aspirated. Then, again 9.3 parts by weight of sodium
30 carbonate are bound onto the effervescent grain surface. After another final drying, the product is removed through a sieve.

b) Preparation of the granulated antifoaming agent

35 In a vacuum mixing tank with a jacket temperature of 80°C, 7.7 parts by weight of sorbitol powder are added and heated to 50°C. Then, 0.2 parts by weight of simethicone in a 30%

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butanone/acetone mixture (5:3) are aspirated in, stirred by vibrational mixing and dried under full vacuum down to 15 mbar at a temperature of at least 45°C.

5 c) Preparation of the total mixture

In a mixer, 20 parts by weight of cimetidine, with 21.1 parts by weight of sorbitol powder if desired, are mixed for 10 minutes at 6 rpm with 178.4 parts by weight of the effervescent system prepared in a). Then 7 parts by weight of the antifoaming agent granules prepared in b) and screened through a 0.6 mm sieve, and 4.5 parts by weight of lemon flavoring, are added, mixed for another 5 minutes at 6 rpm. The final mixture is pressed into tablets which weigh 2.3 g, contain 200 mg of cimetidine, and have a hardness of 6-8 kp.

Example 2: Preparation of effervescent tablets containing 200 mg of cimetidine, and citric and malic acid in the effervescent grains:

102 parts by weight of coarse citric acid, 25 parts by weight of powdered citric acid and 1.1 parts by weight of malic acid are heated to 60°C with stirring in a preheated vacuum tank. A solution consisting of 0.4 parts by weight of water, 0.22 parts by weight of sorbitol and 0.22 parts by weight of malic acid is then aspirated in and distributed onto the citric acid by mixing. 52.5 parts by weight of sodium bicarbonate and 4.4 parts by weight of aspartame are next added to the mixture and dried by stirring, in a vacuum of up to 200 mbar. Next, 1.9 parts by weight of sodium carbonate are aspirated in and distributed in the mixture by stirring, and then vacuum drying is performed down to 15 mbar. Finally, a final drying can be performed with ethanol, and then 9.3 parts by weight of sodium carbonate are added to the mixture. The rest of the procedure is similar to Example 1.

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Example 3: Effervescent tablets containing 400 mg of cimetidine, and mannitol as a neutral substance

5 49 parts by weight of citric acid are aspirated into a preheated vacuum tank and heated with stirring to 60°C. Then, 0.45 parts by weight of a solution 1, which has been prepared from 0.25 parts by weight of water and 0.20 parts
10 by weight of mannitol, is aspirated in and distributed on the citric acid by mixing, whereupon 14.7 parts by weight of sodium bicarbonate and 3.2 parts by weight of aspartame are then added. Reaction is started with stirring and then drying is performed with a vacuum up to 200 mbar. 0.5 parts
15 by weight of sodium carbonate are next aspirated and distributed in the mixture by stirring, and then drying is performed with a vacuum to 15 mbar. Then 0.5 parts by weight of a solution 2, which has been prepared from solution 1 by the addition of 0.16 parts by weight of monosodium citrate,
20 is aspirated into the mixture and distributed by mixing. The effervescent grains obtained therefrom are then dried by vacuum and stirring to 20 mbar, and finally 2.8 parts by weight of sodium carbonate are added. To this mixture is then added 17.3 parts by weight of cimetidine, 4.3 parts by
25 weight of mannitol, 8 parts by weight of sorbitol, 0.9 parts by weight of flavoring, and 4 parts by weight of antifoaming agent granules prepared according to Example 1 b), until distribution is uniform.

30

Example 4: Effervescent tablets containing 300 mg of cimetidine, as well as maltodextrin as a neutral substance.

35 Similarly to Example 3, for a 300 mg cimetidine effervescent tablet, a 50% solution of maltodextrin is selected, which is

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then used in the same amount as in the case of the 400 milligram form.

In all of the examples in which the tablets contain 100 to 400 mg of cimetidine, the tablet weight can be 2.3 g. The tablets have a dissolving time of preferably 60 to 150 seconds and a buffering capacity below 5 meq, measured according to USP XXII, by back-titration (with 0.5 N NaOH) of an effervescent tablet dissolved in 70 ml of water and with 30 ml of 1.0 N HCl added.

The figures given in the following table 1 are the percentages of individual ingredients in the particular total mixture of the illustrated preferred embodiments, which therefore are in the following preferred ranges:

Table 1

Cimetidine	2 - 30%	(cooresponds to an effervescent tablet containing 50 to 600 mg of cimetidine)	
Citric acid	30 - 60%	sorbitol	5-20%
Sodium bicarbonate	10 - 30%	mannitol	2-10%
Sodium carbonate	2 - 10%	simethicone	0.005-0.5%
Aspartame	1-4%	flavoring	0.1-3%

A preferred percentage composition of cimetidine effervescent tablets or bags of granules containing 100, 200, 300 and 400 mg of cimetidine, with a total weight of 2.31 grams, is summarized below in table 2:

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Table 2

	100 mg	200 mg	300 mg	400 mg
Cimetidine	4.30	8.70	13	17.3
Citric acid	50	50	48.2	48.2
Sodium citrate	0.04	0.04	0.04	0.04
Aspartame	1.74	1.64	2.54	3.24
Sorbitol	12.5	12.5	12.8	8.00
Sodium bicarbonate	20.7	20.7	14.7	14.7
Sodium carbonate	4.4	4.4	3.5	3.3
Manntiol	4.3		4.3	4.3
HMA Lemon flavoring	2.0	2.0	0.9	0.9
Simethicone	0.02	0.02	0.02	0.02

5 Example 5: Cisapride effervescent tablets

a) Preparation of the effervescent grains

655 parts by weight of crystalline citric acid, 70 parts by weight of citric acid powder and 8 parts by weight of sodium saccharin sodium are heated while mixing to 60°C. Then 2.8 parts by weight of a solution consisting of 0.6 parts by weight of sorbitol, 0.3 parts by weight of trisodium citrate, 0.5 parts by weight of citric acid and 1.6 parts by weight of water are aspirated into this mixture and distributed by mixing. Next, 340 parts by weight of sodium bicarbonate as well as 2 parts by weight of aspartame are added and reacted. Before drying, 77 parts by weight of sodium carbonate are added, whereupon the mixture is vacuum dried with slow stirring to 15 mbar.

- 20 -

b) Preparation of the granulated drug

Insoluble and hydrophobic cisapride is attached to a suspending substance by means of a binder and a small amount of a tenside as follows: A solution of 10 parts by weight of cisapride, 2 parts by weight of polyvinylpyrrolidone and 0.8 part by weight of docusate sodium in 1 part by weight of ethanol and 40 parts by weight of acetone is applied to 10 parts by weight of Aerosil^(R), uniformly distributed and then dried while stirring. The granules are sieved to 0.1 - 0.3 mm.

c) Preparation of the final mixture

To 1152 parts by weight of effervescent grains are added 50 parts by weight of maltodextrin, 100 parts by weight of lactose, 184 parts by weight of mannitol, 40 parts by weight of flavoring, 50.2 parts by weight of anti-foaming granules (0.2 parts by weight of simethicone coated onto 50 parts by weight of mannitol), as well as the granulated drug prepared in b), mixing is carried out for 15 minutes for uniform distribution and the mixture is then pressed to form tablets of 1.6 g, which have an acid-binding capacity of only 2 meq. Cisapride effervescent tablets having such a low acid-binding capacity are unknown to date.

25

Example 6: Beta-carotene effervescent tablets

With this extremely acid- and oxidation-sensitive substance, attention must be paid to an especially good covering of the acid. The surface and the contact zone on the beta-carotene must be kept alkaline. Therefore the effervescent grains are covered at least in part with calcium carbonate, thus insuring an alkaline surface. This, however, does result in a slightly longer dissolving time, which in this case is desirable, because the beta-carotene needs time to suspend while the tablet is dissolving. Large amounts of sorbitol, as in US-A-5 223 264 mentioned at the outset, are by no

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means suitable for a beta-carotene effervescent tablet which is intended to be dissolved or suspended in water.

a) Preparation of the effervescent grains

5 1315 parts by weight of citric acid, 7 parts by weight of sodium saccharin and 45 parts by weight of sodium cyclamate are heated in a vacuum tank to 50°C. Then 16.8 parts by weight of a solution prepared from 3.6 parts by weight of calcium carbonate, 19 parts by weight of citric acid, 12
10 parts by weight of sorbitol, and 45 parts by weight of water are stirred in and distributed onto the citric acid by mixing. Next, 400 parts by weight of calcium carbonate and 190 parts by weight of citric acid are added and the mixture heated with stirring to 60°C. Then follows the second
15 granulation with 44 parts by weight of the above-mentioned solution, and after distributing and mixing, 403 parts by weight of sodium bicarbonate are added, and also, before drying, 52 parts by weight of sodium carbonate. The mixture is then vacuum-dried to 15 mbar with slow mixing.

20

b) Preparation of the final mixture

130 parts by weight of sorbitol and 540 parts by weight of mannitol and 50 parts by weight of flavoring, an encapsulated beta-carotene suspendable in water and
25 corresponding to 2 to 15 parts by weight of 100% beta-carotene, plus, if desired, 50 to 250 parts by weight of vitamin C and/or a solid tocopheryl acetate suspendable in water (corresponding to 10 to 75 parts by weight of 100% tocopheryl acetate), plus still other vitamins if desired,
30 are mixed with 2415 parts by weight of the effervescent grains prepared according to a). The product has a tablet weight of 3.3 g and its dissolving time is 60 to 90 seconds.

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Example 7: Ranitidine effervescent tablets

a) Preparation of the effervescent grains

840 parts by weight of crystalline citric acid, 210 parts by
5 weight of citric acid powder, 45 parts by weight of sodium
cyclamate, and 4 parts by weight of sodium saccharin are
heated in a vacuum mixing tank at 60°C. Then a solution
consisting of 6 parts by weight of water, 1 part by weight
of sodium citrate, and 3 parts by weight of sorbitol is
10 aspirated in and distributed by stirring. 500 parts by
weight of sodium bicarbonate are next added and allowed to
react, and thereafter 370 parts by weight of monosodium
citrate are added, which are also allowed to react. Lastly,
100 parts by weight of sodium carbonate are added and the
15 granules are dried with slow stirring up to 15 mbar.

b) Preparation of the final mixture

To the effervescent grains thus prepared, 167 parts by
weight of ranitidine hydrochloride, 125 parts by weight of
20 mannitol plus 100.4 parts by weight of a granulated
antifoaming agent (consisting of 100 parts by weight of
mannitol and 0.4 parts by weight of simethicone) and the
flavoring agent are added. This mixture is mixed for 15
minutes for uniform distribution, and then pressed to
25 tablets of 2.5 g. The tablets have a dissolving time of 60
to 80 seconds and an acid-binding capacity of about 2 meq
and contain (in percent by weight) 6.8 ranitidine
hydrochloride, 42.0 citric acid, 14.8 monosodium citrate,
20.0 sodium bicarbonate, 4.0 sodium carbonate, 2.0
30 sweeteners, 5.0 mannitol, 0.1 sorbitol, 4.0 granulated
antifoaming agent (containing 0.016 diemthylpolysiloxane)
and 1.2 flavoring.

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Example 8:

545 parts by weight of crystalline citric acid and 133 parts by weight of powdered citric or tartaric acid are mixed while heating to 60°C. Then, as the first coating, a solution which consists of 6 parts by weight of water and 4 parts by weight of sorbitol is distributed on the surface by stirring. Next, 222 parts by weight of sodium bicarbonate are made to react on the surface of the citric acid, and finally 80 parts by weight of sodium bicarbonate are added. The product is dried with slow stirring. The granules are screened to 1.5 mm, and then mixed for 10 minutes at 10 rpm with 167 parts by weight of ranitidine hydrochloride, 100 parts by weight of anti-foaming granules (containing 0.4 parts by weight of simethicone and 100 parts by weight of lactose), plus 54 parts by weight of sweetener and 40 parts by weight of flavoring, until uniform distribution is obtained. The mixture is then pressed to tablets weighing 1.43 g and having a dissolving time of 65-70 sec, a hardness of 8, and an acid-binding capacity of about 1.5 meq. The product contains no monosodium citrate. Ranitidine effervescent tablets having such a low acid-binding capacity have not been disclosed to date.

25

Example 9:

38.2% of citric acid is heated with 0.26% of sodium saccharin to 60°C, then two-thirds of a solution which consists of, with respect to the final mixture, 0.6% water, 0.18% sorbitol, and 0.12% sodium citrate is applied. The solution is distributed for 5 minutes by mixing at 10 rpm. Then 16.2% of sodium bicarbonate and 2.9% of aspartame are added and anchored on the surface of the citric acid by reaction on the neutral substance coating. Then follows a second wetting with the third one-third of the solution; then 12.9% monosodium citrate and, finally, 5.2% sodium

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carbonate are added. The effervescent grains are dried while mixing them slowly by applying a vacuum, at a temperature of at least 50°C, to 15 mbar. The basic effervescent granular product is screened to 1.5 mm and mixed with 11.0% of
5 ranitidine hydrochloride, 6.5% of mannitol, 6.5% of anti-foaming granules plus 0.2% of flavoring, and pressed to tablets of 1.55 g, which have a dissolving time of 50 sec at a hardness of 7.3 and an acid-binding capacity of less than 2 meq.

10

Example 10: Vehicle crystal grains coated only with a neutral substance

15 Since cisapride, for example, in comparison to ranitidine, is not as highly sensitive to acid, it is nevertheless also possible by the procedure to be described below to achieve protection against the acid, all the more so since the drug is embedded in granules.

20

a) Preparation of the acid crystals coated with a neutral substance

593 parts by weight of crystalline citric acid plus 70 parts by weight of citric acid powder are heated to 60°C. Then a
25 solution of 4 parts by weight of sorbitol in 4 parts by weight of water is applied and distributed onto the surface of the citric acid by mixing. Finally the citric acid thus coated is vacuum dried at 50 to 60°C.

30 In the case of both the form of effervescent product presented here and that of effervescent grains which contain a second alkali or alkali earth carbonate coating, it is possible to protect cisapride, for example, against attack by the citric acid in the drug granules by the addition of
35 sodium bicarbonate.

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b) Preparation of the drug granules

- 160 parts by weight of mannitol, 10 parts by weight of cisapride, 5 parts by weight of aerosil and 10 parts by weight of sodium bicarbonate are heated with mixing to 60°C.
- 5 Then half of a solution of 27 parts by weight of methyl ethyl ketone (or 45 parts by weight of acetone), 2 parts by weight of alcohol, 2 parts by weight of poly(vinyl pyrrolidone) K30, 1 part by weight of propylene glycol and 0.8 parts by weight of docusate sodium are added and
- 10 distributed for 5 minutes for the purpose of uniform wetting. The mixture is dried to 0.8 bar, the second part of this solution is aspirated, and again distributed by stirring for 5-10 minutes, and finally vacuum dried.
- 15 The active agent granules are then screened to 0.3 mm and already have an enhanced protection against acid attack simply due to the sodium bicarbonate they contain. They can then be mixed with the acid crystals coated with neutral substance, the remaining carbonates and bicarbonates, as
- 20 well as the other tablet ingredients, and pressed to give tablets.

c) Preparation of the final mixture

- The citric acid dried and coated according to a) is then
- 25 mixed with the drug granules prepared according to b), 50 parts by weight of sweetener, 80 parts by weight of sodium carbonate, 430 parts by weight of sodium bicarbonate, and 50 parts by weight of maltodextrin, 100 parts by weight of lactose, 150 parts by weight of mannitol, 50 parts by weight
- 30 of an antifoaming granulate, and 20 parts by weight of flavoring, and then pressed to tablets of about 1.6 g, which have a dissolving time of 60 to 70 seconds at a hardness of 7.

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Example 11: Cisapride effervescent tablets

a) Preparation of the effervescent granules:

Citric acid, consisting of an amount of 300 parts by weight
5 of granules, 80 parts by weight of fine granules and 40
parts by weight of powder, together with 5 parts by weight
of saccharin sodium, is uniformly wet at 60°C with 2.2 parts
by weight of a solution which contains 0.4 part by weight of
sorbitol, 0.15 part by weight of sodium bicarbonate, 0.45
10 part by weight of citric acid and 1.2 parts by weight of
water. 12 parts by weight of malic acid are then aspirated
in and uniformly anchored on the sorbitol layer formed on
the citric acid crystals. Finally, 205 parts by weight of
sodium bicarbonate and 1.2 parts by weight of aspartame are
15 aspirated in and once again uniformly distributed. Finally,
the material is covered with 46 parts by weight of sodium
carbonate, vacuum-dried and discharged through a 1.2 mm
sieve.

20 b) Preparation of the active ingredient granules:

12 parts by weight of polyvinylpyrrolidone are dissolved in
12 parts by weight of ethanol; 6 parts by weight of
propylene glycol and 6 parts by weight of docusate sodium
are then added and the mixture is diluted with 165 parts by
25 weight of ethyl methyl ketone. Half of this solution is
distributed over a mixture of 960 parts by weight of
mannitol, 30 parts by weight of Aerosil^(R), 60 parts by
weight of sodium bicarbonate and 61 parts by weight of
cisapride, which is heated to 60°C. Partial drying is then
30 carried out in vacuo, and further wetting is effected with
the second half of the solution, followed by complete drying
and discharge through a 0.3 mm sieve.

The final mixture is prepared analogously to Example 5.

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Claims

1. A granular effervescent product suitable for preparing an aqueous solution or suspension of one or more pharmaceutically active substances for oral administration, being capable of being pressed into tablets, and/or said product in tablet form, comprising effervescent grains obtained from carrier crystals of at least one solid, edible organic acid which are substantially covered by at least one coating containing at least one neutral substance soluble in water and/or alcohol, wherein said neutral substance is effective for depressing the melting point of the acid crystals on their surface, and at least one substance selected from the group consisting of alkali carbonate, alkali bicarbonate, alkaline earth carbonate, alkaline earth bicarbonate, alkali salt of at least one solid edible organic acid, alkaline earth salt of at least one solid edible organic acid is applied onto said coating.
2. The granular product or tablet according to claim 1, wherein the neutral substance is selected from the group consisting of a water-soluble polymer, a higher alcohol, a carbohydrate and a hydrocolloid, and which neutral substance is present in an amount of from about 0.05 to about 1.0 % by weight, preferably from about 0.07 to about 0.8 % by weight.
3. The granular product or tablet according to claim 1 or 2, wherein a moisture-binding agent is anchored on said effervescent grains, which moisture-binding agent preferably is selected from the group consisting of anhydrous sodium carbonate and sodium sulfate and preferably is applied in an amount of from about 4 to about 10 % by weight with respect to the total mixture.
4. The granular product or tablet according to any one of the preceding claims, wherein on the effervescent grains at least one additional coating is applied, comprising a sub-

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stance selected from the group consisting of alkali salts and/or alkaline earth salts of at least one solid, edible, organic acid as buffer and, optionally, comprising an additional neutral substance, and wherein preferably at least one of the coatings contains an antifoaming agent.

5. The granular effervescent product or tablet according to any one of the preceding claims, wherein the granular product, or said granular product compressed in tablet form, further comprises at least one antifoaming agent present in a granular product of its own.

6. The granular product or tablet according to claim 4 or 5, wherein the antifoaming agent is selected from the group consisting of dimethicone and simethicone and is applied in an amount of from about 0.005 to about 0.5 % by weight with respect to the total mixture or from about 0.05 to about 2.0 % by weight with respect to the pharmaceutically active substance.

7. The granular product or tablet according to any one of the preceding claims, wherein it has an acid-binding capacity of less than 5, preferably less than 3 meq, measured according to USP XXII.

8. The granular product or tablet according to any one of the preceding claims, wherein, at a total weight of no more than 2.5, preferably no more than 2.0 grams, in water at room temperature, it has a dissolving time of less than 180, preferably less than 120 seconds.

9. The granular product or tablet according to any one of the preceding claims, comprising a pharmaceutically active substance which is hydrophobic and wherein the hydrophobic substance is present in granules separate from the effervescent components, in which granules the hydrophobic substance is coated or anchored onto at least one substance

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selected from the group consisting of suspending agents - preferably selected from the group consisting of Aerosil(R) and Avicel(R) - and neutral substances - preferably selected from the group consisting of mannitol and sorbitol.

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10. The granular product or tablet according to claim 9, wherein the granules also contain at least one component selected from the group consisting of binders - preferably polyvinylpyrrolidone (PVP) -, small amounts of a tenside - preferably selected from the group consisting of dioctyl sodium sulfosuccinate and sodium lauryl sulfate -, alkali and/or alkaline earth carbonate and/or bicarbonate.

11. The granular product or tablet according to any one of the preceding claims, wherein it contains, with respect to the total mixture, about 2 to about 30 % by weight of cimetidine; about 30 to about 60 % by weight of a solid, edible organic acid; about 12 to about 40 % by weight of at least one alkali or alkaline earth carbonate or bicarbonate (of which about 2 to about 10 % by weight is sodium carbonate as moisture-binding agent); about 1 to about 4 % by weight of a sweetener; about 0.01 to about 30 % by weight of a neutral substance (of which about 0.01 to about 0.05 % by weight is for the neutral substance coating), preferably about 3 to about 20 % by weight of sorbitol and about 2 to about 10 % by weight of mannitol; about 0.005 to about 0.5 % by weight of an antifoaming agent, and about 0.1 to about 3 % by weight of flavoring agent.

12. The granular product or tablet according to any one of claims 1 to 10, wherein it contains, with respect to the total mixture, the following components: about 0.4 to about 4.5 % by weight of cisapride; about 0.4 to about 4.5 % by weight of suspending agent; about 0.1 to about 1 % by weight of binder, preferably polyvinylpyrrolidone (PVP); about 0.03 to about 0.35 % by weight of tenside, preferably dioctyl sodium sulfosuccinate; about 30 to about 55 % by weight of a

- 30 -

solid, edible organic acid, preferably citric acid; about 12 to about 40 % by weight of at least one alkali or alkaline earth carbonate or bicarbonate (of which about 2 to about 10 % by weight is sodium carbonate as moisture-binding agent);
5 about 0.3 to about 2.5 % by weight of sweetener; about 0.02 to about 55 % by weight of neutral substance (of which about 0.02 to about 0.1 % by weight is for the neutral substance coating), preferably selected from the group consisting of maltodextrin, lactose and mannitol; about 0.005 to about
10 0.05 % by weight of antifoaming agent, preferably selected from the group consisting of dimethicone and simethicone; and about 0.2 to about 5 % by weight of flavouring.

13. The granular product or tablet according to any one of
15 claims 1 to 10, wherein it contains, with respect to the total mixture, the following components:

- about 0.1 to about 0.5 % by weight of beta-carotene (100%);
- about 0 to about 2 % by weight of tocopheryl acetate
20 (100%);
- about 35 to about 70 % by weight of solid, edible organic acid, preferably about 0 to about 10 % by weight of ascorbic acid, about 35 to about 55 % by weight of citric acid, and about 0 to about 5 % by weight of malic acid;
- 25 - about 11 to about 38 % by weight of at least one alkali or alkaline earth carbonate or bicarbonate, preferably about 5 to about 15 % by weight of calcium carbonate and about 5 to about 20 % by weight of sodium bicarbonate;
- about 1 to about 4 % by weight of sweetener;
- 30 - about 0.1 to about 35.0 % by weight of neutral substance (of which about 0.1 to about 0.5 % by weight is for the neutral substance coating), preferably about 1 to about 10 % by weight of sorbitol and about 5 to about 25 % by weight of mannitol; and
- 35 - about 0.3 to about 3 % by weight of flavouring.

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14. The granular product or tablet according to any one of claims 1 to 10, wherein it contains, with respect to the total mixture, the following components : about 3 to about 14 % by weight of ranitidine hydrochloride (75 - 300 mg per dose); about 30 to about 50 % by weight of citric acid; about 0 to about 20 % by weight of monosodium citrate; about 10 to about 30 % by weight of sodium bicarbonate; about 2 to about 10 % by weight of sodium carbonate; about 1 to about 3 % by weight of sweetener; about 0.05 to about 0.2 % by weight of neutral substance for the first coating as well as about 0 to about 15 % by weight of additional neutral substances; about 0 to about 8 % by weight of antifoaming granules, and about 0.1 to about 4 % by weight of flavoring.
15. 15. An effervescent tablet containing at least one pharmaceutically active substance and an effervescent system comprising at least one solid, edible, organic acid, at least one alkali metal carbonate or bicarbonate as a gas-forming component and at least one alkali metal salt of the acid, at least two layers being applied to carrier crystals consisting of the at least one acid, wherein the first layer contains at least one other, solid, edible, organic acid or the alkali metal salt of this other acid, or both, whereas the second layer contains at least one alkali metal salt of said at least one acid, and wherein the first layer additionally contains a neutral substance selected from the group consisting of a water-soluble polymer, a higher alcohol, a carbohydrate and a hydrocolloid.
16. 16. A granular product or tablet with an effervescent system and cisapride as the pharmaceutically active substance, wherein, at a total weight of less than 2 grams, preferably less than about 1.6 grams, it has an acid-binding capacity of less than 5 meq, preferably less than 3 meq.

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17. A granular product or tablet with an effervescent system and cimetidine as the pharmaceutically active substance, wherein, at a total weight of less than 2.5 grams, preferably less than about 2.0 grams, it has an acid-binding capacity of less than 5 meq, preferably less than 3 meq.

18. A granular product or tablet with an effervescent system and ranitidine as the pharmaceutically active substance, wherein, at a total weight of less than 2.6 grams, preferably less than 2.0 g, it has an acid-binding capacity of less than 3 meq, preferably less than 2 meq.

19. A method for the preparation of a granular product or of a tablet according to any one of the preceding claims, wherein crystals of at least one solid, edible organic acid are wet with an aqueous solution of a neutral substance, and then, before complete drying, an alkali and/or alkaline earth carbonate and/or bicarbonate in powder form is uniformly distributed and anchored on the moist surface layer by mixing, whereupon the effervescent grains thus prepared are dried and mixed with a pharmaceutically active substance - preferably with an acid-sensitive one, especially one that is selected from the group consisting of H₂-blockers, cimetidine, ranitidine, cisapride and beta-carotene - and pharmaceutically acceptable adjuvants, and optionally compressed into tablets.

20. The method according to claim 19, wherein, on the effervescent grains, at least one additional coating is applied by wetting the grains with the solution of a buffer substance, preferably one that is selected from the group consisting of alkali carbonate, alkali bicarbonate, alkaline earth carbonate, alkaline earth bicarbonate, alkali salt of at least one solid edible organic acid and alkaline earth salt of at least one solid edible organic acid.

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21. The method according to claim 19 or 20, wherein the solution further comprises a neutral substance selected from the group consisting of a water-soluble polymer, a higher alcohol, a carbohydrate and a hydrocolloid.

5

22. The method according to any one of claims 19 to 21, wherein, in addition to the drug, the effervescent grains are also mixed with a granular product which has been made by applying an antifoaming agent in an appropriate solvent to the surface of neutral substance particles, and drying the solvent.

23. The method according to any one of claims 19 to 22, wherein the dried effervescent grains are wetted with ethanol, which preferably contains an antifoaming agent dissolved, and are dried again, by evaporating the ethanol, to remove residual moisture.

24. The method according to any one of claims 19 to 23, wherein the pharmaceutically active substance, before admixing it to the effervescent system, is - together with a binding agent and/or a tenside - applied in solution to and uniformly distributed on the grains of a suspension agent and dried.

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25. The method according to any one of claims 19 to 24, wherein the pharmaceutically active substance, before admixing it to the effervescent system, is mixed with at least one neutral substance, at least one suspension agent and at least one substance selected from the group of alkali carbonate, alkali bicarbonate, alkaline earth carbonate, alkaline earth bicarbonate, alkali salt of at least one solid edible organic acid, alkaline earth salt of at least one solid edible organic acid, whereafter a solution of at least one binding agent and/or a tenside is at least once applied to, distributed on the grains of the mixture and dried.

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26. A process for the manufacture of effervescent granules from a powdered or granular mixture of a solid, edible, organic acid and the carbonate and/or bicarbonate of an alkali and/or alkaline earth metal under vacuum, wherein,
5 for the passivation of the surface of at least one of the components to a state of strong inertia to the reaction, there is added to the heated mixture during the treatment under vacuum a metered quantity of a polar solvent, the difference in pressure caused by development of carbon di-
10 oxide through the addition of solvent during the reaction being determined up to a maximum of 1000 mbar, the volume and mass of the carbon dioxide liberated being ascertained from this difference in pressure, and the heat treatment being repeated, after rapid drying of the mixture, as many
15 times as necessary to obtain passivation of the surface as indicated by an evident slowing down of the reaction and by a reduced development of gas, and wherein in said polar solvent there is dissolved a neutral substance selected from the group consisting of a water-soluble polymer, a higher
20 alcohol, a carbohydrate and a hydrocolloid.

27. A process for the preparation of an effervescent granular material containing at least one solid, crystalline edible organic acid and at least one carbonate of an alkali
25 metal or an alkaline earth metal which splits off CO₂ upon reaction with said organic acid in aqueous solution, which comprises:

- pre-reacting a portion of said organic acid and said carbonate in solution in water and/or alcohol to form a pre-
30 reaction product,
- adding said pre-reaction product to an additional portion of said organic acid in crystalline form with thorough mixing to form a first coating by reaction with said organic acid crystals and liberation of the resulting water of
35 crystallization,

- 35 -

- applying at least one additional coating including said carbonate onto the organic acid crystals with said first coating adhering thereto, and
 - terminating the reaction after the last coating has been applied by drying, wherein to said pre-reaction product
- 5 there is added a neutral substance selected from the group consisting of a polymer soluble in water and/or alcohol, a higher alcohol, a carbohydrate and a hydrocolloid.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 95/00650

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 00886 (GERGELY) 21 January 1993 cited in the application see page 17 - page 18; examples 6,7 ---	1-27
A	EP,A,0 415 326 (SS PHARMACEUTICAL CO., LTD.) 6 March 1991 cited in the application see the whole document ---	1-27
A	US,A,4 704 269 (KORAB) 3 November 1987 see column 6 - column 7; example 1 ---	1-27
A	GB,A,1 270 781 (ABBOTT LABORATORIES) 12 April 1972 cited in the application see the whole document -----	1-27

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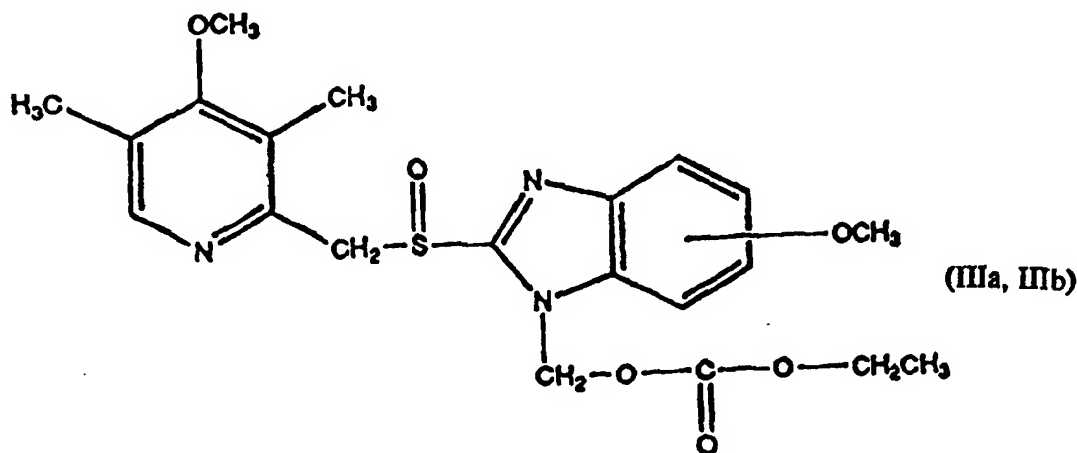
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(54) Title: NOVEL ETHOXYCARBONYLOXYMETHYL DERIVATIVES OF SUBSTITUTED BENZIMIDAZOLES



IIIa (+)-enantiomer

IIIb (-)-enantiomer

(57) Abstract

The novel optically pure compounds, i.e. the single enantiomeric compounds, (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (-)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

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NOVEL ETHOXYCARBONYLOXYMETHYL
DERIVATIVES OF SUBSTITUTED BENZIMIDAZOLES

Field of the invention

The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation.

Background of the invention

The compound 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, having the generic name omeprazole is described in EP 5129. Omeprazole is an effective gastric acid secretion inhibitor, and is useful as an antiulcer agent.

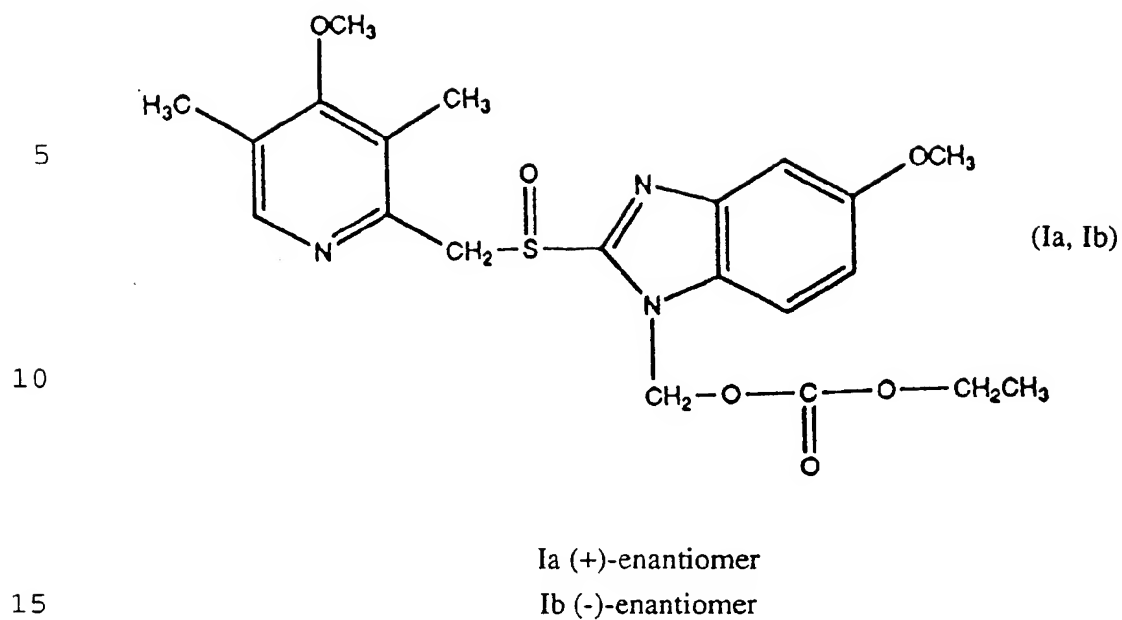
A number of alkoxycarbonyloxymethyl derivatives of omeprazole are disclosed in EP 0233284. The compounds, omeprazole as well as its N-substituted derivatives, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as lower degree of interindividual variation. The present invention provides such compounds, which are novel single enantiomers of ethoxy-carbonyloxymethyl derivatives of omeprazole.

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution.

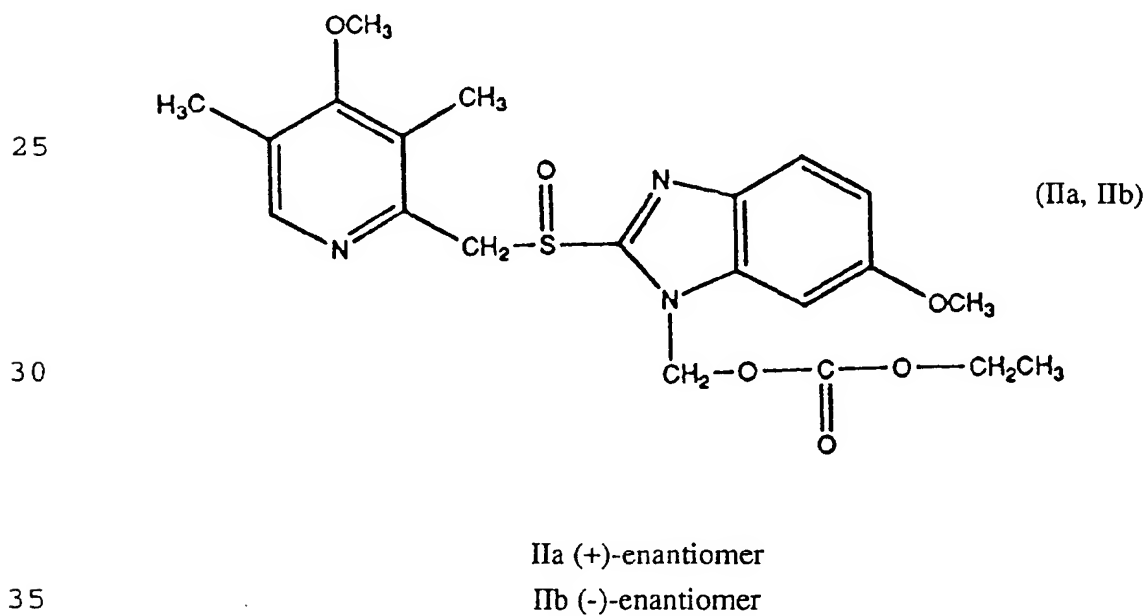
There is no example given in the prior art of the isolated and characterized compounds of the invention.

Detailed description of the invention

The present invention refers to the new single enantiomers of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate according to compounds Ia and Ib

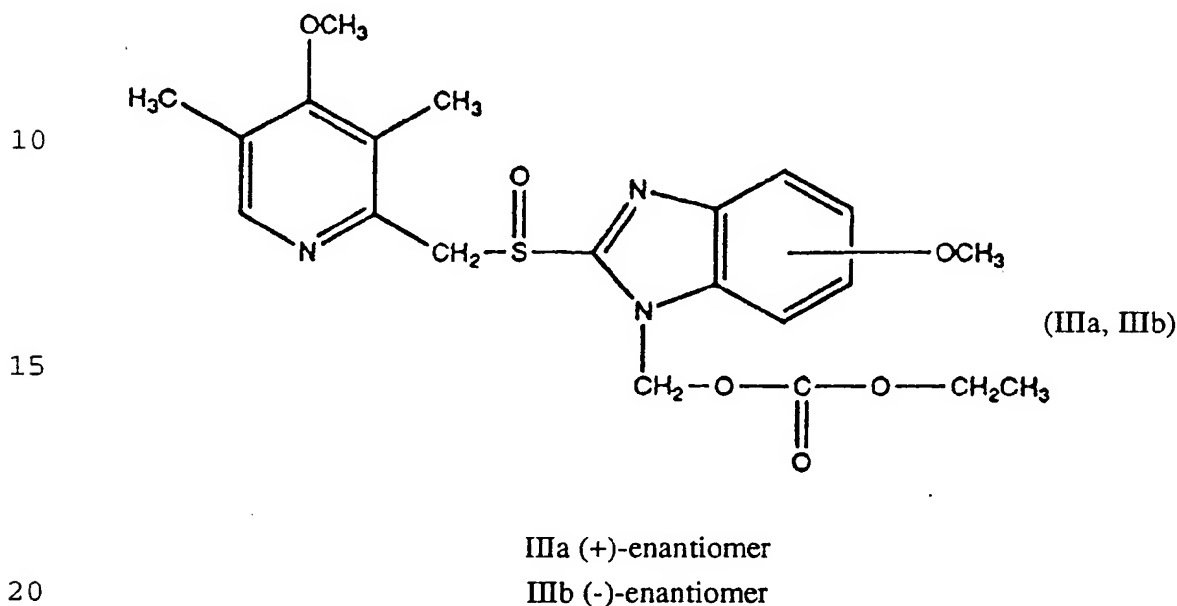


20 as well as the new single enantiomers of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate according to compounds IIa and IIb.



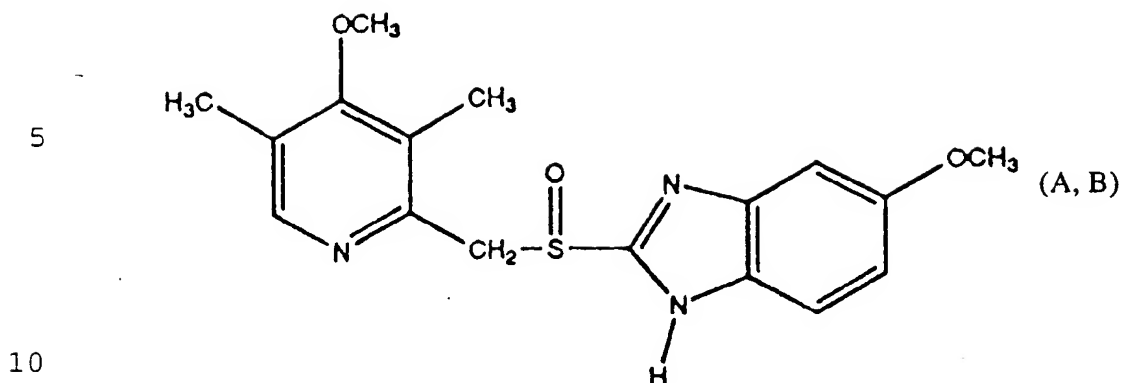
The invention also refers to the new single enantiomers of the regioisomeric mixture

of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate according to compounds IIIa and IIIb, wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.



With the expression "optically pure compound of the invention" is meant the (+)-enantiomer of said compound (or compounds) essentially free of the corresponding (-)-enantiomer and the (-)-enantiomer essentially free of the corresponding (+)-enantiomer, respectively.

It is believed that the compounds of invention is metabolized into the corresponding compounds, carrying H in the N-1 position in the benzimidazole nucleus (compounds A and B, i.e. the single enantiomers of omeprazole) before exerting its effect.



A (+)-omeprazole

B (-)-omeprazole

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Single enantiomers of omeprazole in neutral form (i.e. not as salts thereof) have hitherto only been obtained as syrups and not as crystalline products. However, the optically pure N-ethoxycarbonyloxymethyl derivatives, both the single enantiomers of pure regioisomers (i.e. the 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate isomer and the 6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate isomer) as well as the single enantiomers of regioisomeric mixtures are obtained as crystalline products.

25

Therefore, it is possible to obtain crystalline products, which would be easier to handle (use) in the preparation of pharmaceutical formulations than a syrup of the single enantiomers of omeprazole in neutral form.

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Further, it is possible to use the single enantiomers of ethoxycarbonyloxymethyl derivatives of omeprazole to obtain the single enantiomers of omeprazole in neutral form in a higher purity.

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The optically pure compounds do not undergo directly racemization in neutral pH, which was surprising since N-substituted omeprazole derivatives, catalyzed by protons, are converted to achiral sulfenic acids which easily undergo the reverse reaction back to sulfoxides (see *e.g.* Brändström *et al.* Acta Chemica Scandinavica 43 (1989) 587). It is obvious that such a reversible reaction from an achiral sulfenic acid back to a sulfoxide would cause a racemic compound. This high stability towards

racemization in neutral pH combined with the assumption that the compounds will be dissolved and converted to optically pure omeprazole in the intestine but not in the acidic compartments of the stomach makes it possible to use a single enantiomeric compound of invention in therapy.

5

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the single enantiomeric compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and goar. The compounds of the invention may also be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections.

20

Preparation

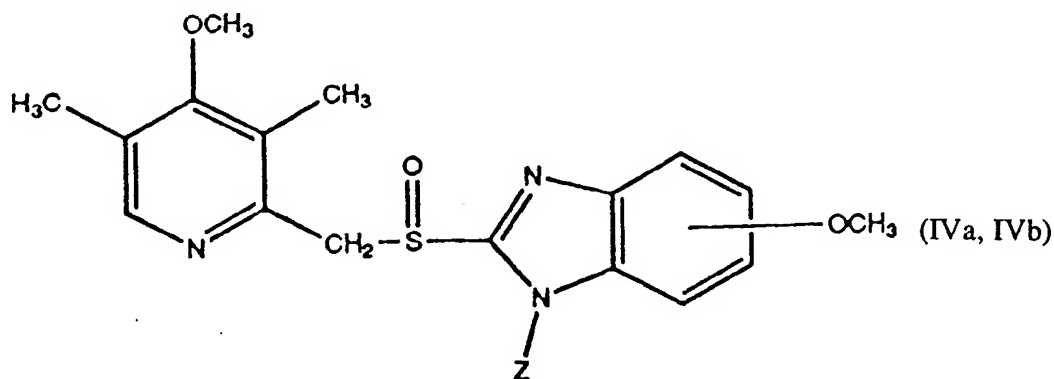
The optically pure compounds of the invention, i.e. the single enantiomers may be prepared according to one of the following methods a), b) or c) described below.

25

a) Reacting a compound of the formula IVa) or IVb).

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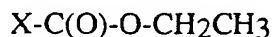
IVa (+)-enantiomers

IVb (-)-enantiomers

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wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6 and wherein Z is either a metal cation such as Na⁺, K⁺, Li⁺ or Ag⁺ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate.

- 10 b) Reacting a compound of the formula IVa) or IVb) either in the form of a pure regioisomer or as a regioisomeric mixture, wherein Z is hydroxymethyl, with a compound of the formula V,

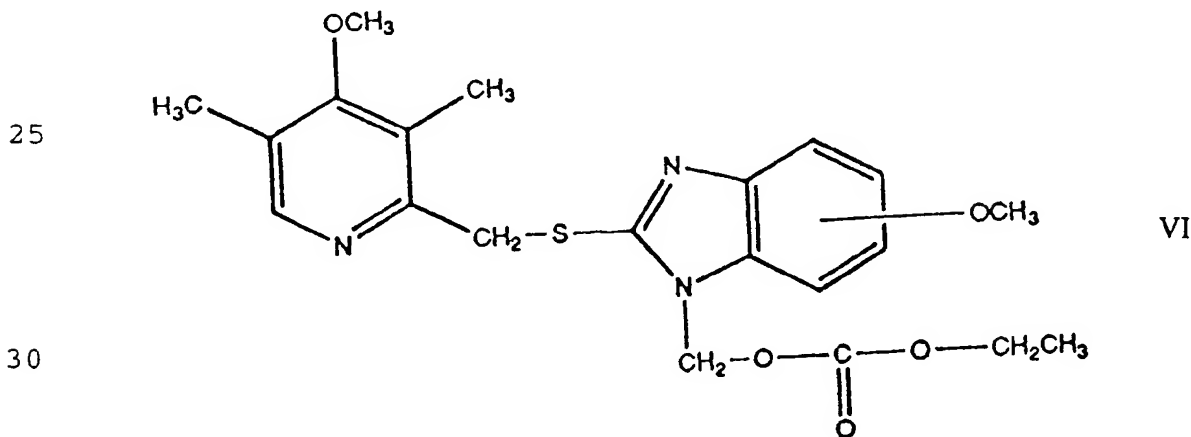


V

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wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

- 20 c) Oxidizing a compound of the formula VI either as a pure regioisomer or as a regioisomeric mixture, wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.



35 This oxidation may be carried out by using a chiral inducing oxidizing agent or by using an oxidizing agent with a chiral catalyst or any other chiral environment such as e.g. chiral solvents.

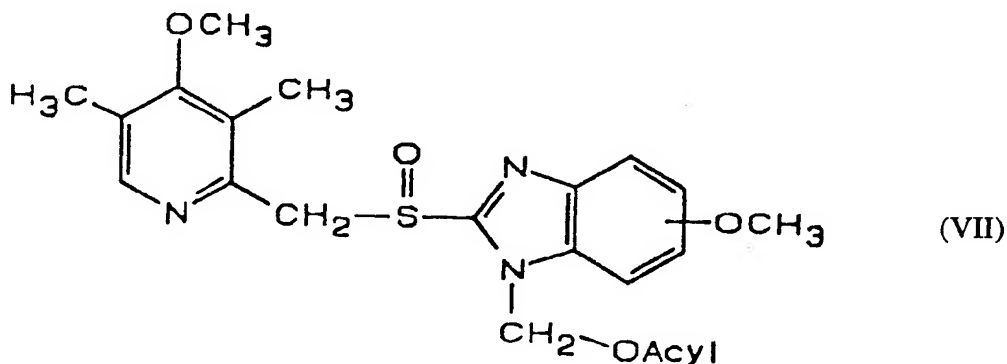
The oxidation may also be carried out enzymatically by using an oxidizing enzyme or

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microbiologically by using a suitable microorganism.

The reactions according to methods a) and b) above are suitably carried out under protective gas in the absence of water. Suitable solvents are acetonitrile, 1-methyl-2-pyrrolidinone, acetone or dimethyl formamide or hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or chloroform. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

The starting compounds IVa) and IVb), respectively, being salt of the single enantiomers of omeprazole, can be prepared by separating the two stereoisomers of a diastereomeric mixture of the following type 5- or 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula VII



wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional

crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an
5 aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the sodium salt of single enantiomers of omeprazole, the resulting compound is treated with a base, such as NaOH, in an aqueous or nonaqueous
10 medium, or with NaOR^2 where R^2 is an alkyl group containing 1-4 carbon atoms, or with NaNH_2 . In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

15 When mixtures of regioisomers are obtained in any of the above methods, a pure regioisomer of a single enantiomer of the invention can be isolated by means of crystallization or chromatography.

In those cases when a mixture of the two enantiomers are obtained, the single
20 enantiomers can be separated according to known methods, e.g. by crystallisation from different solvents.

In some cases the starting materials utilized in the methods a)-c) are unknown. These unknown starting materials may be obtained from known compounds by utilizing
25 processes known per se.

Chloromethyl ethyl carbonate may be obtained from ethanol by treatment with chloromethyl chloroformate in the presence of pyridine.

30 Intermediates of formula IV, wherein Z is hydroxymethyl are obtained by reaction of the corresponding single enantiomer of omeprazole with formaldehyde.

Starting materials of the formula V may be obtained by known methods, e.g. from ethanol by treatment with phosgene or 1,1'-carbonyl diimidazole or p-nitrophenyl
35 chloroformate.

Starting materials of formula IV and VI can be obtained from the regioisomeric mixtures of the corresponding compounds by means of crystallization or

chromatography.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories

which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or
5 they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of
10 the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder
15 to be reconstituted with a suitable solvent prior to use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to
20 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate
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(+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt 3.0 g (8.2 mmol) was dissolved in water (200 ml). The solution was neutralized with an aqueous solution of ammonium chloride and thereafter extracted with methylene chloride. The organic phase was dried over Na₂SO₄, filtered and then removed by film evaporation. The oily residue containing (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in acetonitrile (50 ml). Potassium carbonate (1.2 g, 9.0 mmol) together with chloromethyl ethyl carbonate (1.2 g, 9.0 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water and methylene chloride. The aqueous phase was pH adjusted to pH 9
30
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with aqueous ammonia. The layers were separated and the organic phase was dried over Na₂SO₄. After filtration the solvent was evaporated off. The product which consisted of approximately equal amounts of the two regioisomers was crystallized when a small amount of acetonitrile was added. There was obtained 3.3 g (90%) of the title compounds as white crystals m.p. 81-96°C. $[\alpha]^{20}_D = -121.4$ (c=1%, chloroform).

NMR data are given below

Example 2. Preparation of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

(-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole sodium salt 3.0 g (8.2 mmol) was dissolved in 1-methyl-2-pyrrolidinone (50 ml). Chloromethyl ethyl carbonate (1.2 g, 9.0 mmol) was added and the mixture was stirred over night. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed repeatedly with water and then dried over Na₂SO₄. After evaporation the product was purified by flash chromatography on silica gel with a mixture of acetonitrile/methylene chloride as eluent. The solvents were removed by film evaporation and there was obtained 2.4 g (66%) of the title compounds as white crystals m.p. 83-100°C. $[\alpha]^{20}_D = +122.8$ (c=1%, chloroform).

NMR data are given below

Example 3. Preparation of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

Starting from 2.9 g of the regioisomeric mixture of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-ylmethyl ethyl carbonate from Example 1 the regioisomers of the (-)-enantiomer was separated by repeated recrystallisations from 2-propanol in which the title compound was somewhat less soluble. 76 mg of the title compound containing less than 8% of the other regioisomer was isolated. The product was obtained as white crystals,

m.p. 115-119°C.

NMR data are given below.

5 Example 4. Preparation of (-)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-ylmethyl ethyl carbonate

Starting from 2.9 g of the regioisomeric mixture of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole-1-ylmethyl ethyl carbonate from
10 Example 1 the regioisomers of the (-)-enantiomer was separated by repeated recrystallisations from 2-propanol in which the title compound was somewhat more soluble. 30 mg of the title compound containing less than 8% of the opposite
15 regioisomer was isolated. The product was obtained as white crystals, m.p. 97-100°C.

NMR data are given below.

Table 1.

20

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data δ ppm</u>
1.	CDCl ₃ 300 MHz	1.3 (m, 3H), 2.2-2.3 (m, 6H), 3.71 (s, 3H), 3.86 and 3.90 (two singlets, 3H), 4.18-4.27 (m, 2H), 4.88 (d, 1H), 4.98 (d, 1H), 6.37-6.42 (m, 1H), 6.51-6.58 (m, 1H), 6.96-7.26 (m, 2H), 7.53 and 7.67 (two doublets, 1H), 8.16 (s, 1H).
25		
2.	CDCl ₃ 300 MHz	1.3 (m, 3H), 2.2-2.3 (m, 6H), 3.70 (s, 3H), 3.84 and 3.89 (two singlets, 3H), 4.17-4.26 (m, 2H), 4.87 (d, 1H), 4.97 (d, 1H), 6.36-6.42 (m, 1H), 6.50-6.57 (m, 1H), 6.95-7.26 (m, 2H), 7.53 and 7.67 (two doublets, 1H), 8.15 (s, 1H).
30		
3.	CDCl ₃ 300 MHz	1.28 (s, 3H), 2.20 (s, 3H), 2.24 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.21 (q, 2H), 4.87 (d, 1H), 4.97 (d, 1H), 6.38 (d, 1H), 6.52 (d, 1H), 7.05 (dd, 1H), 7.24 (d, 1H), 7.53 (d, 1H), 8.15 (s, 1H).
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4. CDCl_3 1.30 (s, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 3.70 (s, 3H),
500 MHz 3.90 (s, 3H), 4.23 (q, 2H), 4.88 (d, 1H), 4.97 (d, 1H),
6.41 (d, 1H), 6.55 (d, 1H), 6.98 (dd, 1H), 7.10 (d, 1H),
7.67 (d, 1H), 8.16 (s, 1H).

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Preparation of the starting compounds used in Examples 1 and 2 are described in the following examples. Further some intermediates used in said preparation of the starting compounds are described by examples.

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Example 5. Preparation of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-
methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was
dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M
sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-
homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1
ml) and the mixture was stirred at ambient temperature over night. The formed
precipitate was filtered off and washed with ether. There was obtained 51 mg (46%)
of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical
purity (e.e.) which was analyzed by chiral column chromatography was $\geq 99.8\%$.
 $[\alpha]_D^{20} = +42,8^\circ$ (c=0.5%, water).

NMR data are given below.

Example 6. Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (+)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-
methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was
dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M
sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-
homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1
ml) and the mixture was stirred at ambient temperature over night. The formed
precipitate was filtered off and washed with ether. There was obtained 56 mg (51%)
of the title compound as white crystals m.p. (decomposition) 247-249°C. The optical
purity (e.e.) which was analyzed by chiral column chromatography was $\geq 99.8\%$.

$[\alpha]_D^{20} = -44.1^\circ$ (c=0.5%, water).

NMR data are given below.

5 Table 2

Ex.	Solvent	NMR data ppm
5.	DMSO-d ₆ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
6.	DMSO-d ₆ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

Example 7. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloxyloxymethyl]-1H-benzimidazole

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A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over MgSO₄ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

30

NMR data are given below.

Example 8. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloxyloxymethyl]-1H-benzimidazole

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The diastereomers of the title compound in Example 7 were separated using reversed

phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na₂SO₄ and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below.

Example 9. Preparation of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 7. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

Example 10. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 9 were separated using reversed phase chromatography (HPLC) in the same way as in Example 8, but using the diastereomeric mixture of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 8. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below.

Example 11. Preparation of (-)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na₂SO₄ and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]^{20}_D = -155^\circ$ (c=0.5%, chloroform).

NMR data are given below

Example 12. Preparation of (+)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na₂SO₄ and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]^{20}_D = +157^\circ$ (c=0.5%, chloroform).

NMR data are given below

Table 3.

	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data ppm</u>
5			
	7.	CDCl ₃ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
10			
	8.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
15			
	9.	CDCl ₃ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
20			
	10.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
25			
	11.	CDCl ₃ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
30			
	12.	CDCl ₃	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.20 (s, 1H).
35			

The best mode of carrying out the invention known at present is to use the compounds described in Example 3 and Example 4.

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

5 Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

10	Compounds according to Example 1	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05 g
15	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compounds was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Tablets

25 A tablet containing 50 mg of active compound was prepared from the following ingredients:

	I	Compounds according to Example 2	500 g
30		Lactose	700 g
		Methyl cellulose	6 g
		Polyvinylpyrrolidone cross-linked	50 g
		Magnesium stearate	15 g
		Sodium carbonate	6 g
35		Distilled water	q.s.
	II	Hydroxypropyl methylcellulose	3 g
		Polyethylene glycol	19 g

Colour Titanium dioxide	4 g
Purified water	313 g

I Compounds according to Example 2 was mixed with lactose and granulated
5 with a water solution of methyl cellulose and sodium carbonate. The wet mass was
forced through a sieve and the granulate dried in an oven. After drying the granulate
was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was
pressed into tablet cores (10.000 tablets), each tablet containing 50 mg of active
substance, in a tableting machine using 7 mm diameter punches.

10

II A solution of hydroxypropyl methylcellulose and polyethylene glycol in
purified water was prepared. After dispersion of titanium dioxide the solution was
sprayed onto the tablets I in an Accela CotaR, Manesty coating equipment. A final
15 tablet weight of 125 mg was obtained.

Capsules

20 Capsules containing 30 mg of active compound were prepared from the following
ingredients:

Compounds according to Example 2	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
25 Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

30 The active compound was mixed with the dry ingredients and granulated with a
solution of disodium hydrogen phosphate. The wet mass was forced through an
extruder and spheronized and dried in a fluidized bed dryer.

35 500 g of the pellets above were first coated with a solution of hydroxypropyl
methylcellulose, 30 g, in water, 600 g, using a fluidized bed coater. After drying, the
pellets were coated with a second coating as given below:

Coating solution:

	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	600 g
5	Ethanol	200 g

The final coated pellets were filled into capsules.

Suppositories

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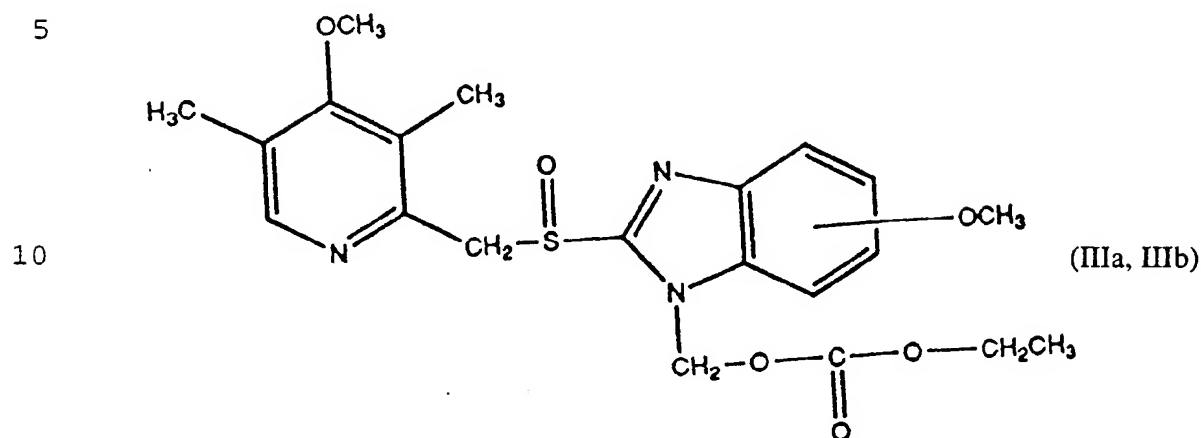
Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

	Compounds according to Example 1	4 g
15	Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each
20 suppository contained 40 mg of active compound.

Claims

1. Single enantiomeric compounds having the formula IIIa and IIIb



IIIa (+)-enantiomer

IIIb (-)-enantiomer

- 20 wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.
2. Compounds according to claim 1, characterized in that the compounds are (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (-)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.
- 30 3. Compounds according to claim 1 characterized in that the compounds are (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.
- 35 4. Compounds according to claim 1 characterized in that the compounds are (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

5. Compound according to claim 1 characterized in that the compound is (-)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (+)-enantiomer.

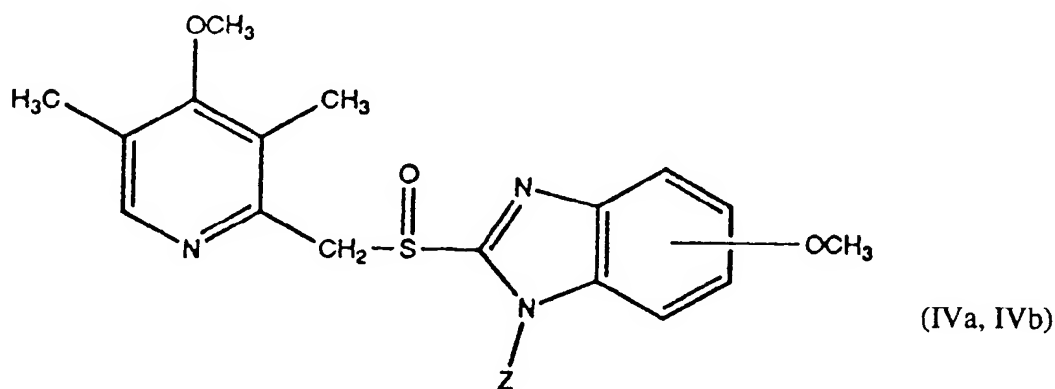
6. Compound according to claim 1 characterized in that the compound is (-)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (+)-enantiomer.

7. Compound according to claim 1 characterized in that the compound is (+)-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (-)-enantiomer.

8. Compound according to claim 1 characterized in that the compound is (+)-6-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (-)-enantiomer.

9. A process for the preparation of compounds according to claim 1 characterized by

a) reacting a compound of the formula IVa) or IVb)

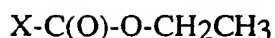


IVa, (+)-enantiomers

IVb, (-)-enantiomers

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6,
and wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary
ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate,

- 5 b) reacting a compound of the formula IVa) or IVb) either in the form of a pure
regioisomer or as a regioisomeric mixture, wherein Z is hydroxymethyl, with a
compound of the formula V,

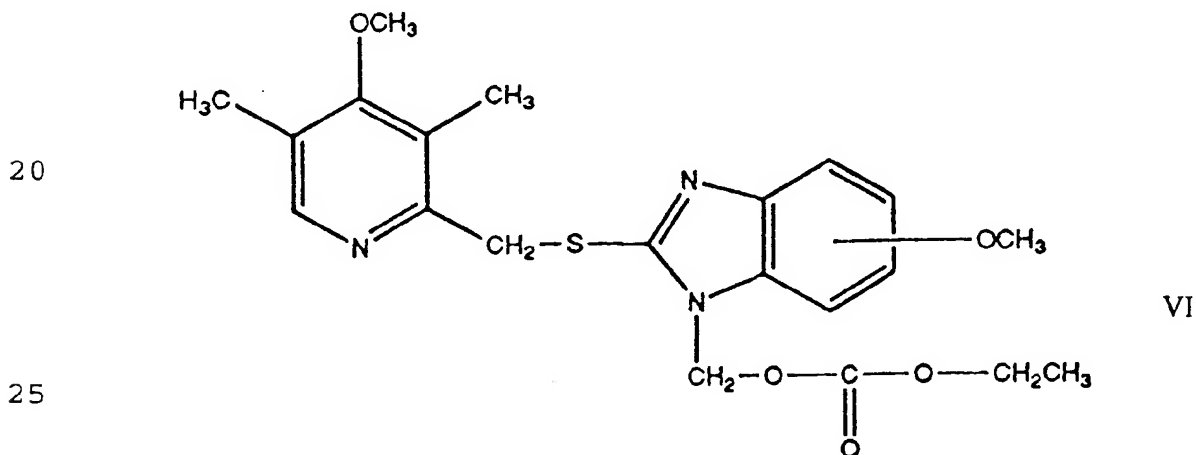


V

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wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in
the presence of a suitable base such as triethylamine, or

- 15 c) oxidizing a compound of the formula VI either as a pure regioisomer or as a
regioisomeric mixture,



- 30 and when mixtures of regioisomers are obtained in any of the above methods the pure
regioisomeric compound is isolated by crystallisation or chromatography.

10. Pharmaceutical preparation comprising a single enantiomeric compound
according to any of claims 1-8 as active ingredient.

35

11. Single enantiomeric compounds according to any of claims 1-8 for use in
therapy.

12. Use of a single enantiomeric compound according to any of claims 1-8 in the manufacture of a pharmaceutical formulation for inhibiting gastric acid secretion.

5 13. Use of a single enantiomeric compound according to any of claims 1-8 for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

10 14. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.

15 15. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00512

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5021433 (T.B. ALMINGER ET AL), 4 June 1991 (04.06.91) -----	1-13

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 November 1994

Date of mailing of the international search report

13 -01- 1995

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-15
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,
see Rule 39.1
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/10/94

International application No.

PCT/SE 94/00512

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5021433	04/06/91	AU-B- 598491	28/06/90
		AU-A- 6542986	19/05/87
		CN-B- 1022487	20/10/93
		DE-A- 3686483	24/09/92
		EP-A- 0221041	06/05/87
		EP-A,B- 0233284	26/08/87
		SE-T3- 0233284	
		ES-T- 2051696	01/07/94
		FI-C- 91151	25/05/94
		JP-T- 63501151	28/04/88
		WO-A- 8702668	07/05/87
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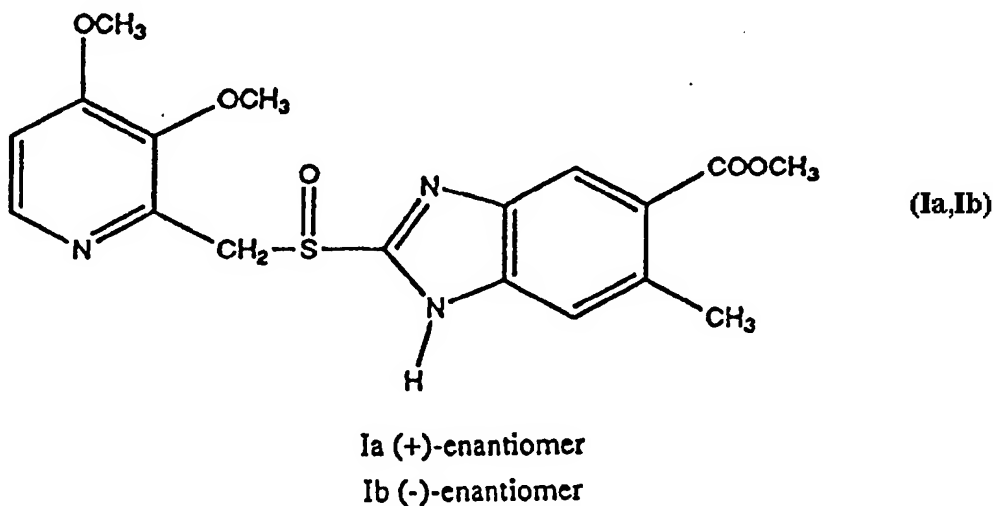
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/12, A61K 31/44		A1	(11) International Publication Number: WO 95/32959
			(43) International Publication Date: 7 December 1995 (07.12.95)
(21) International Application Number: PCT/SE95/00519		(74) Common Representative: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	
(22) International Filing Date: 11 May 1995 (11.05.95)			
(30) Priority Data: PCT/SE94/00511 27 May 1994 (27.05.94) WO (34) Countries for which the regional or international application was filed: AT et al.		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(60) Parent Application or Grant (63) Related by Continuation US 08/256,171 (CIP) Filed on 27 May 1994 (27.05.94)		Published With international search report.	
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): LINDBERG, Per, Lennart [SE/SE]; Gundas gata 40, S-431 51 Mölndal (SE). SUNDÉN, Gunnel, Elisabeth [SE/SE]; Frigångsgatan 10, S-413 01 Göteborg (SE). VON UNGE, Per, Oskar, Sverker [SE/SE]; Alvågen 4, S-430 33 Fjärås (SE).			

(54) Title: NOVEL DIALKOXY-PYRIDINYL-BENZIMIDAZOLE DERIVATIVES

(57) Abstract

The novel optically pure compounds, i.e. the single enantiomeric compounds, (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole and (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or a therapeutically acceptable salt thereof, such as Na⁺, Mg²⁺, Li⁺, K⁺, Ca²⁺ and N⁺(R)₄ salts, where R is an alkyl group with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.



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NOVEL DIALKOXY-PYRIDINYL-BENZIMIDAZOLE DERIVATIVES

Field of the invention

5 The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

10

Background of the invention

The compound 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole, and therapeutically acceptable salts thereof are described in application number EP 91911618.6. This compound and its therapeutically acceptable salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile. The present invention provides such compounds, which are novel salts of single enantiomers of 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole as well as the novel single enantiomers of the neutral form of said compound.

25

The separation of the enantiomers of therapeutically active sulfoxides, such as substituted benzimidazoles, for example omeprazole (5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19. The isolation of single enantiomers of the sulfoxide agent Ro 18-5364 is described in Euro. J. Biochem. 166 (1987) 453-459. Furthermore, separation of the enantiomers of omeprazole in a preparative scale is described in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, the active compound, omeprazole, is quite sensitive and the acid has to be quickly

35

neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values
5 between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralization will create heat which will be difficult to handle in large scale production.

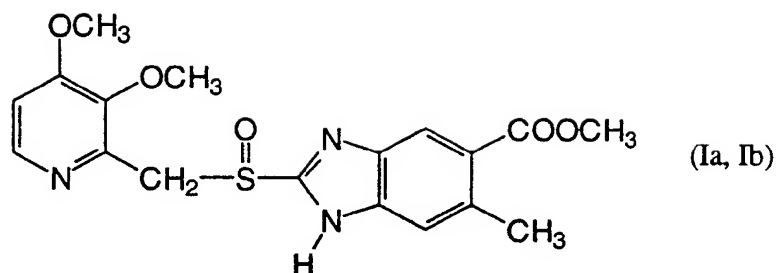
10 The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. Thus, this novel method can be used in large scale to obtain single enantiomers of the compound of the invention in neutral form, as well as in the form of the therapeutically acceptable salts.

15 These novel compounds of the invention, being sulfoxides, could be expected to undergo racemization in neutral pH as well as in basic pH. See for example Brändström et al, Acta Chemica Scandinavia 43 (1989) p.536-547. Surprisingly, the inventors now found that the novel single enantiomers of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole as well
20 as its therapeutically acceptable salts are stable towards racemization.

There is no example known in the prior art of any isolated or characterized single enantiomers of the compound of the invention. Furthermore, the inventors are not aware of any description in the scientific literature of any isolated salt of a single
25 enantiomer of the claimed type.

Detailed description of the invention

30 The present invention refers to the new single enantiomers of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole according to compounds Ia and Ib



Ia (+)-enantiomer

Ib (-)-enantiomer

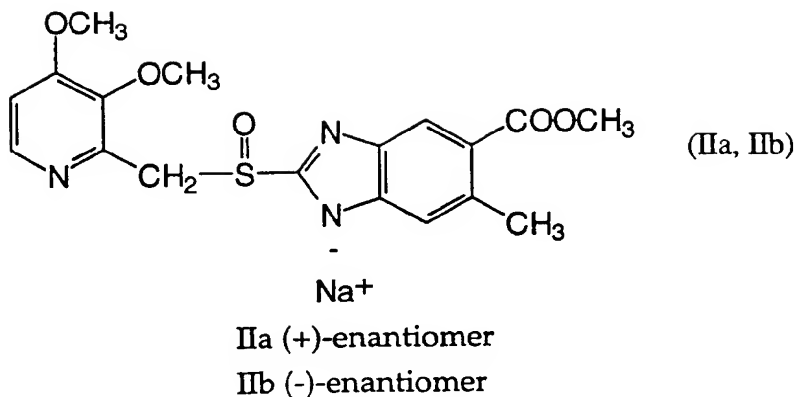
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as well as therapeutically acceptable salts thereof. Such salts are for example the Na^+ , Mg^{2+} , Ca^{2+} , Li^+ , K^+ and $\text{N}^+(\text{R})_4$ salts of the single enantiomers of said compound, where R is an alkyl group with 1-4 carbon atoms, i.e. (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole and (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole as well as Na^+ , Mg^{2+} , Ca^{2+} , Li^+ , K^+ and $\text{N}^+(\text{R})_4$ salts of the single enantiomers, where R is an alkyl group with 1-4 carbon atoms.

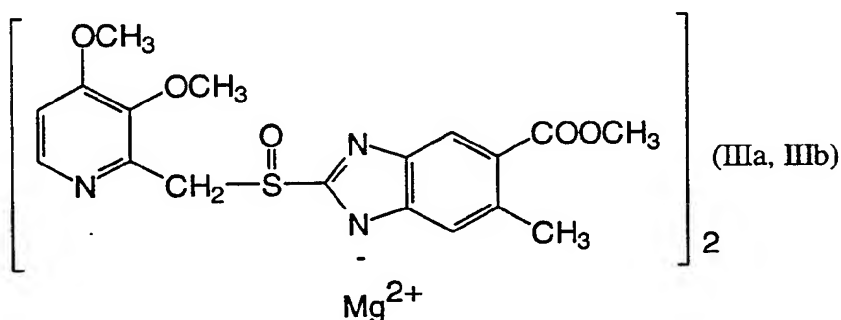
15 Particularly preferred salts of the compound of the invention are the Na^+ , Mg^{2+} and Ca^{2+} salts of the single enantiomers of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole.

20 The most preferred compounds of the invention are the optically pure 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole according to the above formulas Ia and Ib. Further preferred compounds are the optically pure Na^+ salts of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole according to compounds IIa and IIb

25



- 5 and the optically pure magnesium salts of said compounds having the formulas IIIa and IIIb.



- 10 IIIa (+)-enantiomer
IIIb (-)-enantiomer

With the expression "optically pure compound of the invention" is meant the (+)-enantiomer of said compound essentially free from the corresponding (-)-enantiomer and the (-)-enantiomer essentially free from the corresponding (+)-enantiomer, respectively. Thus, every single compound of the invention is obtained in high optical purity. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers, the compounds of the invention are easy to obtain. Moreover, as mentioned above the novel optically pure compounds are stable towards racemization in neutral pH as well as basic pH. The former was surprising since the mechanism of the degradation reactions at neutral pH of these kind of sulfoxides (omeprazole analogues) contains reversible reactions via achiral intermediates (see *e.g.* Brändström *et al.* Acta Chemica Scandinavica 43 (1989) 536-547, especially p.538). It is obvious that such reversible reactions from achiral intermediates back to a sulfoxide would

cause a racemic product. Further, the novel optically pure compounds are stable towards racemization in basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization, both in neutral pH and basic pH, makes it possible to use a single enantiomeric compound of the invention in the neutral form as well as salts thereof in therapy.

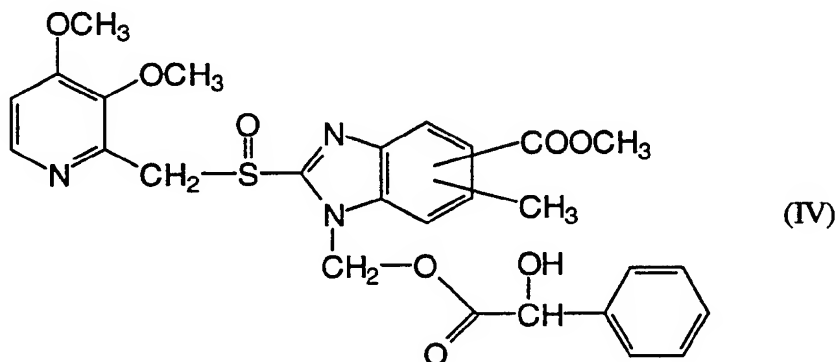
The specific method of preparation of the single enantiomers of the compound of the invention is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomeric compounds in the neutral form as well as the salts thereof.

The single enantiomeric compounds of the invention as well as the racemate have a high level of bioavailability, and does not block the uptake of iodine into the thyroid gland, and still said compounds are very effective as inhibitors of gastric acid secretion and exhibit high stability properties at neutral pH.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the single enantiomeric compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

Yet a further aspect of the invention is the diastereomeric mixture of a regioisomeric mixture having the formula IV, which is an intermediate used in the

specific method of preparation, wherein the carbomethoxy and methyl substituents in the benzimidazole moiety are in the 5 or 6 position, respectively.

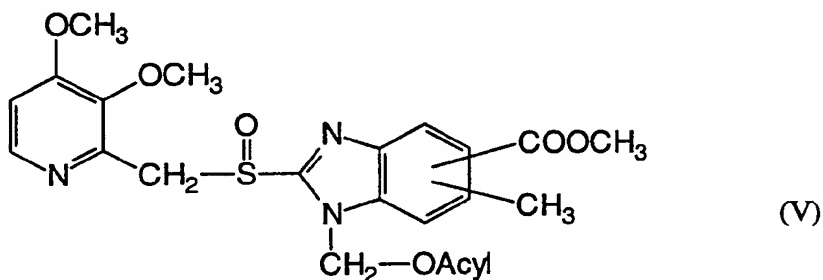


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Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the stereoisomers of a diastereomeric mixture of the regioisomeric mixture of the following type, 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-acyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-acyloxymethyl]-1H-benzimidazole formula V

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wherein the carbomethoxy and methyl substituents in the benzimidazole moiety are in position 5 or 6, respectively, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomeric compounds of the invention in neutral form are then isolated by neutralizing aqueous solutions of the salts of said

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compounds with a neutralizing agent which can be an acid or an ester such as methyl formate.

5 The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

10

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water; or with a base in a mixture of acetonitrile and water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

15

To obtain the optically pure Na^+ salts of the invention, i.e. Na^+ salts of the single enantiomeric compound of the invention, the resulting compound in neutral form is treated with a base, such as NaOH , in an aqueous or nonaqueous medium, or with NaOR^2 wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with NaNH_2 . Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the single enantiomers of the Na^+ salts, to the optically pure Na^+ salts as a syrup are added a mixture of 2-butanone and toluene, but the crystalline form of the single enantiomers of the Na^+ salt may also be prepared by adding NaOH to a mixture of the single enantiomeric compound of invention and a non-aqueous medium, such as a mixture of 2-butanone and toluene.

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To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as MgCl_2 , whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomeric compound of the invention with a base, such as $\text{Mg}(\text{OR}^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH , or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as CaCl_2 .

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Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds IIa and IIb) and the magnesium salts (compound IIIa and IIIb), exemplified by their salts with Li^+ , K^+ , Ca^{2+} and $\text{N}^+(\text{R})_4$, where R is an alkyl group with 1-4 C-atoms.

5

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration. An active compound in a form with high solubility in water is requested for parenteral preparations, for some oral preparations an active compound in a form with low solubility is suitable.

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In the preparation of pharmaceutical formulations in form of dosage units for oral administration the single enantiomeric compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the single enantiomeric compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of

administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

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Example 1. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

- 10 The crude product of the diastereomers of a mixture of two regioisomeric mandelic esters, namely 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (1.8 g, 3.3 mmol) was
- 15 divided into three parts. Each part was chromatographed on a reversed phase column (HPLC, Kromasil C8) in order to separate the diastereomers. The stereoisomers were easily separated by elution with a mixture of aqueous 0.1 M ammonium acetate and acetonitrile (70/30), but each separated diastereomer consisted of a mixture of the two regioisomers. These intermediates were used
- 20 directly in their solutions during the hydrolyses; To the acetonitrile/aqueous solutions of the more lipophilic diastereomer were added 1 M aqueous solutions of NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylenechloride whereupon the
- 25 organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 250 mg of a yellow oil. The product was crystallised by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 171-173° C. [α]_D²⁰ = +153.1° (c=0.5%,
- 30 chloroform).

NMR data are given below.

Example 2. Preparation of (-)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

To the acetonitrile/aqueous solutions of the less lipophilic diastereomer of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole (obtained from the very same reversed phase chromatographic preparations described in Example 1) were added 1.0 M NaOH until the pH was around 12-13. After 5 minutes the solutions were neutralized with 3.0 M aqueous solutions of NH₄Cl. The solutions from each preparation were combined and extracted with methylenechloride whereupon the organic phases were dried over Na₂SO₄. Removal of the solvents and flash chromatography of the residue (silica gel, methanol-methylenechloride gradient 1-8%) yielded 270 mg of a yellow oil. The product was crystallized by adding acetonitrile (3 ml) and after filtration there was obtained 210 mg (32%) of the title compound as white crystals m.p. 173-174° C. [α]_D²⁰ = -150.0° (c=0.5%, chloroform).

NMR data are given below.

Example 3. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a mixture of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.51 mmol) and ethanol (10 ml) was added an aqueous solution of 2.0 M NaOH (0.26 ml, 0.51 mmol). The solvent was removed by film evaporation whereupon the residue was dissolved in 2-butanone (1 ml). Toluene (5 ml) was added dropwise while stirring. The formed precipitate was removed by centrifugation and washed with diethyl ether. There was obtained 170 mg (81%) of the title compound as white crystals m. p. (decomp.) 170°-173°C. [α]_D²⁰ = +93.6° (c=1%, methanol).

NMR data are given below

Example 4. Preparation of (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

To a mixture of (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)-
5 methyl]sulfinyl]-1H-benzimidazole (200 mg, 0.51 mmol) and ethanol (10 ml) was
added an aqueous solution of 2.0 M NaOH (0.26 ml, 0.51 mmol). The solvent was
removed by film evaporation whereupon the residue was dissolved in 2-butanone
(2 ml). Toluene (5 ml) was added dropwise while stirring. The formed precipitate
was isolated by filtration and washed with diethyl ether. There was obtained 200
10 mg (96%) of the title compound as white crystals m. p. (decomp.) 172°-175°C.
[a]²⁰_D = -93.8° (c=1%, methanol).

NMR data are given below

15 Example 5. Preparation of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-
H-benzimidazole sodium salt (100 mg, 0.24 mmol) obtained as in Example 3 was
20 dissolved in water (2 ml) and MgCl₂·6H₂O (25 mg, 0.12 mmol) dissolved in water
(1 ml) was added dropwise. The formed precipitate was isolated by centrifugation
and washed with water. The product was dried in a desiccator and there was
obtained 84 mg (87%) of a white powder. [a]²⁰_D = + 170° (c=0.5%, DMSO).

25 Example 6. Preparation of (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-
benzimidazole sodium salt (100 mg, 0.24 mmol) obtained as in Example 4 was
30 dissolved in water (2 ml) and MgCl₂·6H₂O (25 mg, 0.12 mmol) dissolved in water
(1 ml) was added dropwise. The formed precipitate was isolated by centrifugation
and washed with water. The product was dried in a desiccator and there was
obtained 84 mg (87%) of a white powder. [a]²⁰_D = -178.8° (c=0.5%, DMSO).

Table 1.

	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data d ppm</u>
5	1.	DMSO-d ₆ 300 MHz	2.62 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.68 (s, 2H), 7.09 (d, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.12 (d, 1H), 13.75 (b, 1H).
10	2.	DMSO-d ₆ 300 MHz	2.62 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.68 (s, 2H), 7.09 (d, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.12 (d, 1H), 13.75 (b, 1H).
15	3.	DMSO-d ₆ 300 MHz	2.58 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 4.36 (d, 1H), 4.74 (d, 1H), 7.07 (d, 1H), 7.31 (s, 1H), 8.10 (s, 1H), 8.21 (d, 1H).
20	4.	DMSO-d ₆ 300 MHz.	2.58 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 4.34 (d, 1H), 4.74 (d, 1H), 7.07 (d, 1H), 7.29 (s, 1H), 8.11 (s, 1H), 8.22 (d, 1H).

Preparation of the synthetic intermediates according to the invention will be described in the following example.

25 Example 7. Preparation of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

30 A solution of 0.33 g (8.2 mmol) sodium hydroxide in 1.6 ml water was added to a mixture of 1.4 g (4.1 mmol) tetrabutylammonium hydrogen sulfate and 0.62 g (4.1 mmol) of (R)-(-)-mandelic acid. Chloroform (50 ml) and a mixture of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1-(chloromethyl)-1H-benzimidazole and 6-carbomethoxy-5-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-(chloromethyl)-1H-benzimidazole (as
35 racemates) were added and the mixture was refluxed for 3 hours. The reaction mixture was chilled and then partitioned between ethyl acetate and water. The

layers were separated and the organic phase was washed with water and dried over Na₂SO₄. Removal of solvents yielded a diastereomeric mixture of the two regioisomeric mandelic esters. The crude product was used directly in the chromatographic step where the diastereomers were separated (Example 1 and 2).

5 Yield: 2.4 g, 62%.

NMR data are given below.

Table 2.

10

<u>Ex.</u>	<u>Solvent</u>	<u>NMR data d ppm</u>
7.	CDCl ₃ 500 MHz	2.6-2.8 (m, 3H), 3.8-4.1 (m, 9H), 4.75-4.95 (m, 1H), 5.00-5.15 (m, 1H), 5.3-5.4 (m, 1H), 6.45-6.70 (m, 15 2H), 6.70-6.80 (m, 1H), 7.1-8.4 (m, 8H).

The best mode of carrying out the invention known at present is to use the magnesium salts of the optically pure compounds of the invention, thus the compounds described in Examples 5 and 6.

20

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

25 Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

30	Compound according to Example 1	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05 g
35	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

5

Enteric-coated tablets

10 An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

15	I	Compound according to Example 2	500 g
		Lactose	700 g
		Methyl cellulose	6 g
		Polyvinylpyrrolidone cross-linked	50 g
		Magnesium stearate	15 g
		Sodium carbonate	6 g
		Distilled water	q.s.
20	II	Cellulose acetate phthalate	200 g
		Cetyl alcohol	15 g
		Isopropanol	2000 g
		Methylene chloride	2000 g
25	I	Compound according to Example 2, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet	
30		containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.	
	II	A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela	
35		Cota ^R , Manesty coating equipment. A final tablet weight of 110 mg was obtained.	

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

5

Compound according to Example 3	4 g
Sterile water to a final volume of	1000 ml

10

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 μ m filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

15

Capsules containing 30 mg of active compound were prepared from the following ingredients:

20

Compound according to Example 6	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

25

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

30

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
5	Acetone	200 g
	Ethanol	600 g

The final coated pellets were filled into capsules.

10

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

15

	Compound according to Example 2	4 g
	Witepsol H-15	180 g

20

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

25 Stability towards racemization at different pH:es

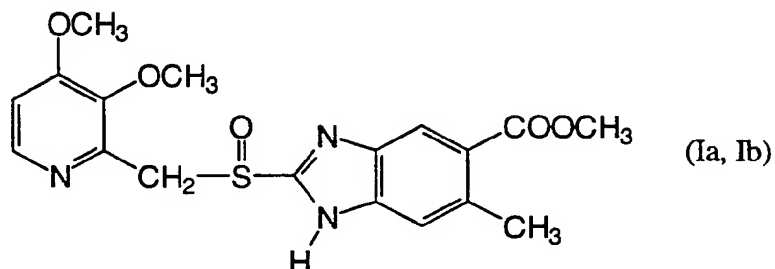
30

The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations (10^{-5} M) at 37°C in aqueous buffer solutions at pH 7 and pH 11. The stereo chemical stability was measured by comparing the optical purity for the (-)-enantiomer of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole in buffer solution immediately after dissolving and after several hours. The surprising high stereo chemical stability in neutral conditions as well as in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained neither at pH 7 nor at pH 11, even after 24 hours. At pH 7, however, the chemical degradation of the compound is much apparent after 28 hours.

35

Claims

1. Single enantiomeric compounds having the formula Ia and Ib



Ia (+)-enantiomer

Ib (-)-enantiomer

- 10 and the therapeutically acceptable salts thereof.

2. Compounds according to claim 1 characterized in that the compound is (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or a therapeutically acceptable salt thereof, substantially free of its (-)-enantiomer.

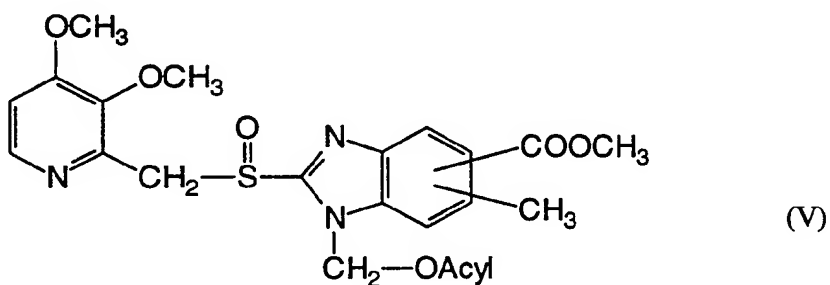
3. Compounds according to claim 1 characterized in that the compound is (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole, or a therapeutically acceptable salt thereof, substantially free of its (+)-enantiomer.

4. Compounds according to any of claims 1-3 characterized in that the therapeutically acceptable salts are Na⁺, Mg²⁺, Ca²⁺, Li⁺, K⁺ and N⁺(R)₄ salts wherein R is an alkyl group with 1-4 carbon atoms.

5. Compounds according to any of claims 1-4 characterized in that the compounds are (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole sodium salt, (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole sodium salt, (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole magnesium salt and (-)-5-

carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole magnesium salt.

6. Compounds according to any of claims 1-3 characterized in that the compounds are (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its magnesium salt and (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its magnesium salt, in their crystalline forms.
7. Compounds according to claims 1 and 2 characterized in that the compound is (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or the magnesium salt thereof, respectively, in its crystalline form substantially free of its (-)-enantiomer.
8. Compounds according to claims 1 and 3 characterized in that the compound is (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or the magnesium salt thereof, respectively, in its crystalline form substantially free of its (+)-enantiomer.
9. Process for the preparation of a compound according to claim 1 characterized in that a diastereomeric ester of formula V



- wherein the carbomethoxy and methyl substituents in the benzimidazole moiety are in the 5 or 6 position, respectively, and wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is subjected to solvolysis with an alkaline solution where the acyloxymethyl group is hydrolyzed off to give the enantiomeric compound in neutral form after neutralization with a neutralizing

agent whereupon the enantiomeric compound in neutral form optionally is converted into a therapeutically acceptable salt.

10. Process according to claim 9 characterized in that the diastereomers
5 are separated by chromatography or fractional crystallization.

11. Process according to claim 9 characterized in that the solvolysis is performed in an alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or
10 dimethylformamide; or a base in a mixture of protic and aprotic solvents, such as water and acetonitrile.

12. Process for the preparation of a compound according to any of claims 1-4 in crystalline form characterized in that a product obtained in claim 9 either
15 neutral form or in the form of a therapeutically salt is treated with a non-aqueous solvent to precipitate the product.

13. Process for preparation of (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its sodium salt and (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its sodium salt in their crystalline forms characterized in that (+)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its sodium salt and (-)-5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-H-benzimidazole or its sodium salt crude product, respectively is treated with a
20 25 non-aqueous medium, such as 2-butanone and toluene.

14. Pharmaceutical preparation comprising single enantiomeric compound according to any of claims 1-8 as active ingredient.

30 15. Single enantiomeric compounds according to any of claims 1-8 for use in therapy.

16. Use of a single enantiomeric compound according to any of claims 1-8 in the
35 manufacture of a pharmaceutical formulation for inhibiting gastric acid secretion.

17. Use of a single enantiomeric compound according to any of claims 1-8 for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.
- 5 18. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.
- 10 19. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.
- 15 20. The compounds 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-[mandeloyloxymethyl]-1H-benzimidazole and 6-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-[mandeloyloxymethyl]-1H-benzimidazole.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00519

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 9119712 A1 (AKTIEBOLAGET ASTRA), 26 December 1991 (26.12.91) --	1-17,20
Y	DE 4035455 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 14 May 1992 (14.05.92) -- -----	9-13,20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

6 Sept. 1995

Date of mailing of the international search report

19.09.1995

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00519

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see Rule 39.1.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/95

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(21) International Application Number: PCT/EP95/02488 (22) International Filing Date: 24 June 1995 (24.06.95) (30) Priority Data: 9413951.6 11 July 1994 (11.07.94) GB (71) Applicant (for all designated States except US): THERAPICON S.R.L. [IT/IT]; Via Malachia Marchesi de Taddei, 21, I-20146 Milan (IT). (72) Inventor; and (75) Inventor/Applicant (for US only): VERONESI, Paolo, Alberto [IT/IT]; Via Malachia Marchesi de Taddei, 21, I-20146 Milan (IT). (74) Agents: HARDISTY, David, Robert et al.; Boulton Wade Tennant, 27 Fumival Street, London EC4A 1PQ (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: A NOVEL DRUG DELIVERY SYSTEM (57) Abstract A pharmaceutical product in unit dosage form and a unit dosage drug delivery system which comprises a multiple layer capsule or housing having two or more layers said layers being of materials, wherein the outer layer possesses a hydrophilic character and the inner layer possesses a hydrophobic character, and wherein there is in contact with the inner layer one or more drug substances having a hydrophobic character.		

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A NOVEL DRUG DELIVERY SYSTEM

The present invention relates to a unit dosage drug delivery system in the form of a soft capsule of different size, shape and colour, consisting of an external capsule housing having two or more coupled layers, sheaths or films, made from different materials, and of a capsule filling having one or more pharmacologically active drug substances for oral, rectal or vaginal administration, which are admixed, dissolved, suspended or agglomerated in an hydrophobic support, consisting basically of the main suspending agent "silicone resin" and optionally of one or more physiologically acceptable auxiliary ingredients, alike surfactants, disaggregants, linear or ramified aliphatic C₂-C₃ alcohols and their esters, retarding agents or other optional components, and to said pharmaceutical composition resulting thereof and to its method of preparation.

BACKGROUND OF THE INVENTION

Many attempts have been made in the past years to produce pharmaceutical forms, including some type of gelatin capsules and gelloids of gelatin, aiming to incorporate drug substances in the capsule filling, but the protection of the active ingredient has not been satisfactorily solved in case the used drug substance is degradable or unstable in presence of moisture, oxidizing agents or gastric (acid)

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fluid. Different types of gelatin capsules (hard or soft) have been studied by many authors, aiming to mainly protect the active ingredient against the atmosphere, but the results were partially satisfactory. A comprehensive review of different types of soft gelatin capsules has been reported by J.P. Stanley, Part II - Soft Gelatin Capsules of "The Theory and Practice of Industrial Pharmacy", pages 404-420, Edition Lea & Fabiger (Philadelphia), 1976 and by Casadio, "Tecnologia Farmaceutica", pages 705-707, Edition Cisalpino Gogliardica (Milan), 1972. Other authors have described conventional gelatin capsules in various patents as for example: US Patent, number 4,816,259; US Patent, number 3,656,997; US Patent, number 4,690,823; US Patent, number 5,173,304; US Patent, number 3,959,540; US Patent, number 3,432,594.

Described capsule housing conventionally possesses an external shell of which the basic ingredient is gelatin, and in general such capsule may be presented as either hard or soft gelatin capsule, the latter one containing suitable plasticizers. The shell of the conventional gelatin capsules consists of an unique external layer, having uniform composition and thickness, surrounding a capsule filling, which contains the pharmaceutical active drug substance admixed with suitable excipients. Few cases of an external film-coating layer have been also described. The unique external layer of the capsule shell of a conventional soft gelatin capsule contains basically gelatin, but also

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appreciable quantities of water as ingredient. However the presence of a certain amount of water in the conventional soft gelatin capsule housing constitutes a considerable seeking to formulate drugs or their salts, which are soluble in water or degradable in presence of moisture, or from the simple contact with water. In fact, by using the current ingredients and the known production techniques for conventional soft gelatin capsules, it is almost impossible to avoid the contact of the active drug substance, contained in the capsule filling, with the moisture of the gelatin mass of the external shell layer, either during the production steps or during the storage period of the finished capsule, until used for its intended purpose. Moreover, since the shell of the current soft gelatin capsules is containing, in addition to water, also large quantities of plasticizers (glycerol or sugars), conventional additives, including plasticizers, colouring agents, opacifiers and preserving agents, it is also difficult to satisfactorily prevent or to control possible chemical incompatibilities between the active drug substance incorporated in the filling and the ingredients of the capsule housing. Said ingredients may also enhance oxidation, degradation or hydrolysis processes, causing partial or sometime considerable loss of activity of the formulated active drug substance.

Accordingly, a main objective of the present invention is to provide an improved unit dosage drug delivery system in

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the form of a soft capsule, showing superior protection to the active drug substance from moisture, oxidizing agents, possible chemical interactions with other auxiliary or optional ingredients of the capsule housing, its method of preparation and the resulting pharmaceutical compositions of this invention.

SUMMARY OF THE INVENTION

It has now been surprisingly discovered that a unit dosage drug delivery system, having an external capsule housing made from at least two or more coupled layers, sheaths or films, from different materials, and a capsule filling made from "silicone resin", provides a substantially improved soft capsule system to incorporate many pharmaceutically active drug substances presenting formulation or stability problems.

It has further been discovered that such unit dosage drug delivery system : (a) offers to the pharmaceutical active drug substance, incorporated in the capsule filling, an improved protection from atmosphere, oxidation, moisture-induced hydrolytic or degradation processes, (b) permits a capsule filling moisture content less than 1 %, (c) minimizes the diffusion of residual water from the external gelatin capsule housing to the capsule filling or of the water-soluble active drug substances to the outer housing system, (d) covers unpleasant tastes or odours, (e)

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controls or improves efficiently the site of action of the drug, (f) prolongs, when necessary, the release of the active drug substance from the capsule filling and (g) suitably avoids chemical incompatibilities between the active drug substance and the other auxiliary or optional ingredients.

Moreover it has further been observed that the unit dosage drug delivery system of this invention allows to conveniently formulate and deliver some delicate or unstable pharmaceutical drug substances, enhances the protective conditions of the relevant compositions thereof and prolongs also the period of stability of the formulated active drug substance.

TABLE 1 - Conventional soft capsule compared with the unit dosage drug delivery system of this invention.

-Omeprazole : oxidation process during the storage (storage conditions : 6 month at 30° C, Relative Humidity 75 % into an open container).

Product	Colour change of the contained Omeprazole	
	Beginning	After 24 weeks
Conventional soft gelatin capsule (an unique layer capsule housing + Labrafils as suspending agent of the active drug substance)	white	violet-brownish

Unit dosage drug delivery system (multiple layers capsule housing + silicone resin as suspending agent of the active drug substance + sodium laurylsarcosinate. 2 round)	white	white
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TABLE 2 - Conventional soft capsule compared with the unit dosage drug delivery system of this invention containing the same active drug substance

-Percentage of humidity after the production process.

Product	% of humidity of the capsule filling	
	Before capsulation process	After stabilization
Conventional soft gelatin capsule (an unique layer capsule housing + Gelucires as suspending agent of the active drug substance)	0.23 %	3.80 %
Unit dosage drug delivery system (multiple layers capsule	0.08 %	0.11 %

housing + silicone resin as
suspending agent of the active
drug substance. 2 oval)

Unit dosage drug delivery	0.07 %	0.12 %
system (multiple layers capsule		
housing + silicone resin as		
suspending agent of the active		
drug substance. 20 oblong)		

In the conventional soft gelatin capsules, the humidity percentage, during the capsulation process and at the end of the stabilization process, is increased of 16.5 times, because of the water migration from the unique layer of the capsule housing to the capsule filling. This process results not important in the case of the unit dosage drug delivery system of this invention (1.3 times).

DETAILED DESCRIPTION OF THE INVENTION

The unit dosage drug delivery system, according to the instant invention, is a soft capsule having the shell housing consisting of at least two or more coupled layers, sheaths or films from different materials, the outer layer or sheath with hydrophilic character and the inner sheaths or films with hydrophobic character, and a capsule filling with a remarkable hydrophobic properties.

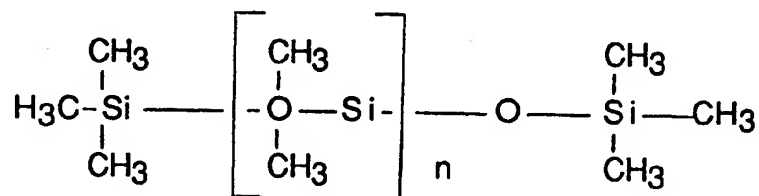
The first outer layer of the capsule housing (hydrophilic layer) is produced by admixing 45 % - 55 % gelatin, 15 % - 30 % glycerin or alternatively 15 % - 30 % modified sorbitol solution at 45 % or their mixture and 35 % - 40 % water into a wet mass, which is thereafter processed into a gelatin ribbon (layer or sheath) of the desired width and thickness (preferably between 0.50 and 1 mm at the wet state) and, after a conventional drying and stabilization process, is containing 60 % - 70 % gelatin, 20 % - 25 % glycerin or modified sorbitol solution or their mixture thereof and 8 % - 10 % water. During the production steps of the wet gelatin mass for the preparation of the first outer layer (hydrophilic layer), conventional additives, plasticizers, colouring agents, opacifiers, preserving agents, antioxidants may be optionally added to the molten mass admixture, without causing any detrimental effect to the resulting gelatin hydrophilic layer. The gelatin mass of the first outer layer is prepared with conventional methods, in a manner that produces a smooth completely dispersed and uniform gelatin molten suspension. The gelatin required for this dispersion should be preferably between 130 and 250 Bloom grams, alkali based skin or bone type, approved for food or pharmaceutical use. Also the other ingredients shall be of pharmaceutical or alimentary use quality, as it may be required by the regulatory authorities. The molten gelatin mass for the preparation of the first outer hydrophilic layer is cooled

and passed on a suitable standard equipment, in order to conveniently prepare a ribbon of gelatin mixture, having the desired width and thickness. In another referred embodiment of this invention, the first outer hydrophilic layer of the capsule housing contains, instead of gelatin, other suitable compounds, alike polyphenyl compounds recently described in literature (Eisai, Korean patent appl. 90-10411 of July 10, 1990), which may substitute gelatin for the manufacturing of conventional soft capsules. The production process is closely comparable to that used for the outer hydrophilic gelatin layer, as previously described. The first outer hydrophilic layer of this embodiment is present in the capsule housing in an amount of from 83.33 % to 99.96 % by weight, preferably between 90 % and 98 %.

The second inner hydrophobic film or sheath of the capsule housing of this invention consists of silicone, of silicone mixture or of other pharmaceutically acceptable silicone polymers of low-medium or medium-high density (silicone hydrophobic film or sheath), or preferably of silicone resin (silicone resin hydrophobic film or sheath), having a suitable intrinsic viscosity varying from 10 to 200,000 cSt ($\text{mm}^2 \times \text{s}^{-1}$).

Silicones are well known polymers widely described in literature. There are different types of polysiloxanes, which are differentiated from the nominal viscosity, represented by an indication following the name of the

substance. More conveniently one group of low-medium density silicones, used in the pharmaceutical and alimentary fields, are dimethyl polysiloxanes (also defined simethicone or dimethicone), which may be also conveniently used for the preparation of the second inner sheath or film of the capsule housing for its chemically inert and hydrophobic character. The most widely used dimethyl polysiloxanes (commonly defined in the European Pharmacopoeia, volume II, page 138 as "dimethiconum" or "dimethicone" and in the French Pharmacopoeia 9.th edition as "low and medium density silicone oils") are dimethyl polysiloxanes (polymers) of linear chain, having the following linear structural formula:



where the degree of polymerization may vary from $n = 20$ to 400, while their nominal cinematic viscosity may vary from $10 \text{ mm}^2 \times \text{s}^{-1}$ to $1000 \text{ mm}^2 \times \text{s}^{-1}$ (from 10 cSt to 1000 cSt). Moreover dimethicone is a product commonly available on the market on its different grades of density. Pharmaceutical grade dimethicone is used for the silicone inner layer of this invention. The thickness of the second hydrophobic inner film or sheath of the capsule housing, made from silicone, silicone mixture or silicone resin,

shall be comprised between 0.1 and 100 microns, preferably between 50 and 80 microns. The selected silicone or silicone mixture shall preferably have a consistence of grease or paste at a temperature of about 37° C. This second inner hydrophobic film or sheath is coupled with the internal face of the first outer hydrophilic layer or sheath, with the conventional methods disclosed in the production process.

In addition to the above components (layers, sheaths or films), the capsule housing may optionally contain an inner additional third or multiple films or sheaths, made from medium-high density silicone polymers or waxes or from jaluronic acid polymers, coupled with the internal face of the said second silicon sheath or film. Another preferred embodiment consists that the additional inner third or multiple films or sheaths are made from silicone waxes, which are non-toxic silicone derivatives, suitable for the preparation of para-medical, and pharmaceutical waxes, known under the trade mark VP 1622 (available from Wacker-Chemie Co) or silicone elastomers RP 73, conform to Pharmacopée Francaise "Silicones-Elastomères" (available from Rhône-Poulenc, Chemical Division, France). The thickness of the additional inner third or multiple films or sheaths of the capsule housing shall be comprised between 0.1 and 100 microns, preferably between 5 and 50 microns. These additional inner hydrophobic films or sheaths from silicone waxes shall be conveniently covered

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with pores, having a desired size (10-100 μm) and distribution (from 2,500 to 25 pores/ mm^2), in order to achieve a retarded diffusion through the pores of the incorporated active ingredient. Another highly preferred embodiment of this invention is that the intrinsic viscosity value of silicone or silicone mixture of the second inner sheath or film of the capsule housing shall be lower than the intrinsic viscosity value of the silicone polymers or waxes of the optional inner third or multiple films or sheaths. More particularly embodiment of this invention is that silicone polymers or waxes and jaluronic acid polymers shall be have peremptorily a melting range of 39° C - 40° C. The sum of the second inner film or sheath and the optional inner third or multiple inner films or sheaths is further comprising of from 0.04 % to 16.67 %, preferably between 2 % and 10 % by weight of the entire capsule housing.

In a preferred embodiment of this invention, the capsule filling comprises one or more pharmaceutical active drug substances admixed, dissolved, suspended or agglomerated in "Silicone Resin", described in the monograph "Silicone Resin" from Japanese "Food Additives", page D-524, which is conveniently reported hereby.

SILICONE RESIN

Description: Silicone Resin occurs as a white to light

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gray, transparent and semitransparent viscous liquid or paste substance without odour.

Identification: Determine the infrared absorption spectrum of Silicone Resin as directed in the liquid film method under the infrared spectrophotometry: it exhibits adsorbances at the wave number of about 2960 cm^{-1} , 1260 cm^{-1} , $1124\text{-}1010\text{ cm}^{-1}$, and 800 cm^{-1} .

Purity: (1) After weight 15 g, put in Soxhlet's extractor. Extract 3 hours by 150 ml of Carbon Tetrachloride. Extraction liquid is evaporated on water bath and use it as test solution : $n_D^{25} = 1.400 - 1.410$. (2) Viscosity of Extracted Silicone oil: 100 - 1,100 cSt (25°C). (3) Specific Gravity: 0.96 - 1.02. (4) Silicon Dioxide (SiO_2): Remaining substance from the extraction should be under 2.25 g after one hour drying at approximately 100°C (15%).

A wide variety of pharmaceutical active drug substances may be incorporated into the capsule filling of this invention at different proportions, varying in the range of from 0.0001 % to 45 % by weight. These individual medicaments and drugs are from all major categories and therapeutic classes, without limitation for human and veterinary use, as for example oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antiseecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, diuretic agents, antineoplastic agents, antiviral nucleosides agents, antifungal agents, analgesics, non steroidal anti-

inflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, central nervous system drugs, organic and inorganic salts, liophylized yeasts and vitamins. The drug is preferably micronized to produce a uniform capsule filling. Micronization is carried out by conventional technique.

The polypeptides, intended for use according to the present invention, is any peptide biologically useful in the cure, mitigation, treatment or prevention of diseases or in the enhancement of desirable physical or mental development and conditions in man or in animals. Polypeptides, especially proteins, for use in human and/or veterinary medicine are of particular interest for this invention due to their instability to the atmospheric agents, alike moisture and oxygen, which may cause their degradation and partial inactivation, which are therefore prevented from the unit dosage drug delivery system of this invention.

The polypeptides intended for use in the methods and compositions of the invention include molecules to which non-peptide prosthetic groups, such as carbohydrates, hemes and fatty acids, have been attached. The polypeptides include molecules made by living organisms or cells, molecules made by synthetic organic chemistry and molecules which are synthetically modified biological products. They may have an amino acid sequence identical

to that of a natural substance or one altered by techniques such as site-directed mutagenesis.

In addition to the covalent (primary) structure, the polypeptides may possess unique conformation (combinations of secondary, tertiary and quaternary structure), which affects their biological functions and physical properties. The considered polypeptides may have important biological functions. They may act as enzymes, enzyme inhibitors, antibodies, antigens, transporters (transporters of electrons, oxygen, metal ions, or small organic molecules), ionophores, antibiotics, mitogens, hormones, growth regulators, neurotransmitters, cell surface recognition proteins, cell chemotactic factors, and cytotoxins. They may also be receptors, agonists, antagonists of the following: ionophores, mitogens, hormones, neurotransmitters, growth regulators, cell surface recognition proteins, cell chemotactic factors and cytotoxins.

Among the polypeptides contemplated by the present invention are therapeutically useful polypeptides such as anti-sera, anti-toxins and antigens and vaccines, including attenuated vaccines (such as those for cholera, influenza, meningitis, pneumonia, poliomyelitis, rabies, typhoid and staphylococcus) and live vaccines (such as those for poliomyelitis, measles, rubella and mumps), growth factors, hormones and like bioactive peptides, as

illustrated by α -1-antitrypsin, atrial natriuretic factor (diuretic), calcitonins, calmodulin, choriogonadotropin (α and β), colony stimulating factor, corticotropin releasing factor, β -endorphin, endothelial cell growth supplement, epidermal growth factor, erythropoietin, fibroblast growth factor, fibronectin, follicle stimulating hormone, granulocyte colony stimulating factor, growth hormone (somatotropin), growth hormone releasing factor (somatoliberin), insulin, insulin-like growth factor (somatomedin), an interferon (typically α , β , γ), an interleukin (typically 1,2,3,4), lutropin, lymphotoxin, macrophage derived growth factor, macrophage inhibiting factor, macrophage stimulating factor, megakaryocyte stimulating factor, nerve growth factor, pancreatic endorphin, parathyroid hormone, platelet derived growth factor, relaxin, secretin, skeletal growth factor, superoxide dismutase, thymic hormone factor, thymic factor, thymopoietin, thyrotropin, transforming growth factor (α and β), tumor necrosis factor, tumor angiogenesis factor, vasoactive intestinal polypeptides and wound angiogenesis factor, immunosuppressives, such as RhO (D) ISG and IVGG's, thrombolytics such as urokinase, streptokinase and tissue plasminogen activator, and antigens such as Rhus all (poison ivy), Rhus tox poison ivy-polyvalent and staphage lysate (staphylococcus lysate).

Other highly preferred polypeptides for use in accordance with this invention are cyclosporins, a group of biologically active metabolites produced by *Tolypocladium inflatum* Gams (formally designed as *Trichoderma polysporum*) and other fungi imperfecti. The major component, cyclosporin A, is a non-polar cyclic oligopeptide with selective immunosuppressive activity very suitable after human organ transplants.

Other polypeptides contemplated by this invention are polypeptides specifically intended for veterinary use, including vaccines, animal growth factors and bovine interferons and interleukin-2. Illustrative vaccines include: bovine vaccines (for example those for anthrax, clostridium (multiple species), pasteurella, leptospira pomona, bovine diarrhoea, brucellosis, parainfluenza, 3-respiratory syncytial virus, tetanus, vesicular stomatitis and staphylococcus), canine vaccines (for example those for bordetella, coronavirus, distemper, parvovirus, parinfluenza and rabies), equine vaccines (for example those for anthrax, encephalomyelitis, influenza, tetanus, rabies and streptococcus-strangles), feline vaccines (such as those for leukemia, pneumonitis-chlamydia and rabies), ovine vaccines (for example those for anthrax, blackleg, bluetongue, enterotoxemia, tetanus and vibriosis) and porcine vaccines (for example those for anthrax, enterotoxemia, dysentery, erysipelas, leptospirosis, parvovirus,

pseudorabies, tetanus and rotavirus).

Yet other polypeptides contemplated for use herein are polypeptides of particular interest in the field of medicine are various enzymes. The enzymes can include labelling enzymes, modifying enzymes, nucleases, polymerases, sequencing enzymes and restriction enzymes. Highly preferred enzymes of the instant invention are lysozyme and digestive enzymes, alike pepsin, enterokinase, trypsin, chymotrypsin, carboxypeptidase, aminopeptidase and elastase (pancreatopeptidase).

Preferred polypeptides for use in accord with the instant invention include growth regulators. Among the preferred growth regulators are hematopoietic factors (which affect the maturation and proliferation of blood cells in lymphoid tissue and bone marrow), cytokines (which generally influence eukaryotic cell growth) and lymphokines (which affect lymphocyte growth). Specific polypeptides, which are growth regulators or lymphokines, are: interleukin 1,2,3 and 4; α , β , and γ interferons; granulocyte colony stimulating factor (G-CSF); granulocyte-macrophage CSF (GM-CSF); macrophage CSF (m-CSF); megakaryocyte CSF; multi CSF or IL-3 (also known as BPA, HCGF, MCGF and PSF); erythropoietin; lymphotoxin; tumor necrosis factor (TNF, also known as cachectin); α and β transforming growth factor (TGF); nerve growth factor (NGF); insulin-like growth factor I and II (IGF I is also called somatomedin C);

growth hormone (GF, also called somatotropin); and growth hormone releasing factor (GHRF, also called somatoliberin). See Clark et al, "The human Hematopoietic Colony Stimulating Factors", Science, 1229-1237 (June 5, 1987); Tanniguchi, "Regulation of Cytokine Expression", Ann. Rev. Imm., 6, 439-464 (1988); and Watson et al., Molecular Biology of the Gene, Vol. II, 4 th Ed., Benjamin/Cummings Publishing (1987).

In another preferred embodiment of this invention, the drug substance consists of prostaglandins, alike prostaglandin A₁, prostaglandin D₂, prostaglandin D₂ analogs, prostaglandin E₁, keto prostaglandin E₁, prostaglandin E₂, methyl prostaglandin E₂, prostaglandin E₃, prostaglandin E_{1α}, prostaglandin F_{2α}, methyl prostaglandin F_{2α}, prostaglandin F_{3α}, prostaglandin H series, prostaglandin X series; prostaciclins, alike prostaglandin I₂, carba prostaglandin I₂, oxo-prostaglandin I₂, and their pharmaceutically acceptable salts or series derivatives, alike misoprostol; tromboxanes, which are hygroscopic and oxidable and their derivatives, alike ifetroban sodium (TXA₂/prostaglandin endoperoxide receptor antagonist), used as antithrombotic agents.

Similarly in another preferred embodiment, the drug substance is consisting of eicosapentaenoic acid (referred also as EPA) and docosahexaenoic acid (referred also as DHA), fatty acids, which are unstable by action of light and

oxygen, formulated alone or added with tocopherol as antioxidant.

In another preferred embodiment the drug substance is represented by H^+/K^+ ATPase inhibitors (benzimidazole derivatives and their pharmaceutically acceptable salts) alike omeprazole, lansoprazole, pantoprazole, pantoprazole sodium, timoprazole, rabeprazole sodium (pariprazole sodium) and other published products under research (search codes: NC-1300, TY-11345), which are not stable in gastric juice and readily oxidable, with macroscopic changes of colour from white to violet-brownish and consequent loss of activity.

Another embodiment for the drug substance capsule filling consists of H_2 -antagonists, alike ranitidine hydrochloride and base, nizatidine, famotidine, which are degraded by atmospheric moisture.

In another preferred embodiment of the unit dosage drug delivery system of this invention, the drug substance consists of antiacids inorganic salts, alike sodium bicarbonate, calcium carbonate and magnesium carbonate .

In another preferred embodiment, the drug substance consists of orally active antiallergic agents, alike astemizole, terfenadine, tranilast, loratadine, azelastine, amlexanox, repirinast, tarzanolast, pemirolast potassium, batebulast HCl, quinolast sodium, suplatast tosylate and other published products under research (search codes: CI-

949, KW-4679, TYB-2285) .

In another preferred embodiment of the unit dosage delivery system of this invention, the drug substance consists of antiasthmatic agents, alike ketotifen, fluoxetine, clemastine fumarate, cetirizine and theophyllinic agents, alike ambuphylline, bamiphylline and oxpentiphylline.

In another preferred embodiment the drug substance consists of orally active inhibitors of angiotensin converting enzyme (ACE), alike captopril, enalapril, lisinopril andtrandolapril, which have an unpleasant odor and scarce stability.

In another preferred embodiment the drug substance consists in diuretic agents, alike indapamide and other aminosulfonic derivatives.

In another preferred embodiment of the unit dosage delivery system of this invention, the drug substance consists of antineoplastic agents, alike etoposide and estramustine phosphate sodium.

In another preferred embodiment the drug substance consists of immunopotentiator agents, alike levamisole.

In another preferred embodiment the drug substance consists of antiviral nucleosides agents, alike acyclovir with inhibitory activity towards several herpes viruses and zidovudine, stavudine, didanosine, for the treatment of adult patients with HIV infection or paediatric patients

(three months to 12 years) with symptomatic HIV infection or with significant HIV-related immunosuppression.

In another preferred embodiment of this invention, the drug substance consists of oral antifungal agents, alike terbinafine, amorolfine, ketoconazole, fluconazole, itraconazole and cilofungin.

In another preferred embodiment of the unit dosage delivery system of this invention, the drug substance consists of antiparkinson agents, alike selegiline, inhibitor of Monoamino-oxidase B (MAO B), and pergolide mesylate, pharmacologically active as dopamine agonist.

In another preferred embodiment of this invention, the drug substance consists of anticonvulsant-antiepileptic agents, alike valproic acid, lamotrigine and felbamate.

In another preferred embodiment the drug substance is represented by antiinflammatory, analgesic, antipyretic agents, which have ulcerative side-effects : aspirin (acetyl salicylic acid), derivatives of indol, alike indomethacin and sulindac, derivatives of oxicam, alike piroxicam and tenoxicam, derivatives of propionic acid, alike pirprofen, ibuprofen, flurbiprofen, ketoprofen, diclofenac, ketorolac, naproxen and indoprofen.

In another embodiment of the unit dosage delivery system of this invention, the drug substance consists of finasteride, an agent used in case of prostatic

hyperthrophy.

In another preferred embodiment of this invention, the drug substance consists of calcium blocking agents, alike nifedipine, isradipine, nicardipine, nilordipine, nimodipine, nisoldipine, furaldipine, clinidipine, efonidipine, elnadipine, amlodipine, nitrendipine, palonidipine, elgodipine, manidipine, benidipine, cronidipine, barnidipine, oxidipine, perdipine, niguldipine, nilvadipine, lacidipine, lidoflazine, cinnarizine, flunarizine and other published products under research, alike darodipine (EN: 090658), arandipine (MPC- 1304) and pranidipine (OPC- 13340).

In another preferred embodiment of the unit dosage drug delivery system, the drug substance consists of cardiovascular preparations, alike nicorandil or diltiazem.

In another preferred embodiment of the unit dosage drug delivery system of this invention, the drug substance is represented by lyophilized yeasts, alike lactobacillus bifidus and lactobacillus bulgaricus, which are not stable in gastric juice. Other optional components in convenient amount may be added to the capsule filling of the instant invention, alike surfactants, such a sorbitan derivative (e.g. polysorbate 80) or sodium lauryl sarcosinate, additional micronized silica gel or lecithin, antioxidants and C₂-C₃ linear or ramified alifatic alcohols, such as absolute ethanol, or polyalcohols and their C₁-C₂ esters.

The antioxidant is hindered phenol, retinoic acid, erythorbic acid, tocopherol, citric acid, and/or anthranilic acid, preferably a retinol acid derivative such as retinol, retinoic acid or its fatty acid esters especially retinylpalmitate. The antioxidant is present at concentrations further comprising of from 0.001 % to 5.0 %, preferably 0.3 % - 0.8 % by weight of the capsule filling. The surfactant concentration may vary from 0.1 % to 2.0 % by weight of the capsule filling. The alcohol or polyalcohol content shall be considered of from 1 % to 30 %, preferably from 10 % to 25 % by weight of the capsule filling. Minor amounts of other materials may be added at art established levels. These include, without limitation, pigments, opacizers, aromes, sweeteners and the like materials, when added, should not interfere with the active drug substance of these compositions. The above optional components or modifications of the capsule filling, consisting basically of drug substance and "Silicone Resin", are intended to improve the acceptability, but are well known within the skill of workers in the pharmaceutical arts and, by themselves, constitute no part of the present invention.

In another preferred embodiment of the unit dosage drug delivery system of this invention consists of rendering gastroresistant the capsule housing after the production process or after any period of storage. The capsule housing of the instant invention, which has been modified to be

rendered gastroresistant, presents for some drug substances the advantage that the capsule filling with the incorporated active drug substance is released (disintegrated) in the intestines, after passing unchanged through the stomach. The techniques used for rendering gastroresistant the soft capsules of the instant invention are very close to those already used for the tablets or gelatin capsules and are within the skill of workers in the pharmaceutical arts and, by themselves, constitute no part of the present invention. The gastroresistance may be obtained by different known methods, according with the specific material of the first outer hydrophilic layer or sheath. Different methods have been also described to produce gastroresistant conventional soft gelatin capsules. Mercer immersed twice the capsules in a solution of beeswax (10% in ether) and then in multiple baths of molten salol (Mercer J., Austral. J. Pharm., 36,1169,1955). Carstensen treats firstly the conventional soft gelatin capsules with a solution at 5 % of HCl and at 5 % of water in isopropanol to have a shiny surface through an hydrolysis. After drying, they are passed in a solution of 3 % of ethylcellulose in isoamyl alcohol. Finally the gelatin capsules are dried by centrifugation (Carstensen J.T., et al., U.S. Patent 2.789.920, April 23, 1957). In British Patent 602,260 the solution of gelatin in aqueous glycerin is added with insoluble organic and inorganic salts of

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cellulose acetate phthalate. The pH of the film shall necessarily be 7 - 7.5. The capsules may be then treated with a solution of 1 % of formaldehyde and then washed and dried. To obtain the gastroresistance, Yen and Stirn immerse, for one minute, under stirring, the capsules in an ethanolic solution of 0.5 % - 10 % of formalin, 0.25 % of resins, alike benzoin and 0.5 % - 3 % of cumarin or vanillin. The solution is eliminated by centrifugation and the capsules are dried (Yen E.C., Stirn F.E., U.S. Pat. 2.727.833,20, December 20, 1955). The unit dosage drug delivery system of this invention may be also conveniently treated with a solution of aldehyde, preferably formaldehyde, in dispersion in a highly volatile water-miscible solvent, preferably acetone. This treatment may be carried out by immersion or by spraying, but preferably by sprinkling the capsules. The ratio of 30 % formaldehyde to acetone is 1:60. The formaldehyde content of the solution is checked at the beginning of the operation and during the process. For this control, may be used the Bougault and Gros method (oxidation with iodine and titration on return of the excess of iodine). The treatment with formaldehyde may be done in order to avoid washing and drying the soft capsules, depending on the degree of gastroresistance and the time of opening in the intestinal juice. The application is obtained in a turbine used for making pills, where internally there are driving, guiding

and acceleration devices for the rotation of the capsules, which are sprinkled by the admission of the solution by means of nozzles or sprinkling roses, opening into the chamber of the turbine. In this manner, the capsules are well wetted by the dispersion of formaldehyde, the acetone evaporates rapidly for the presence of a suction device and the capsules can be immediately packed. Another known method for soft gelatin capsules consists to immerse or spray the first outer hydrophilic layer or sheath for a suitable period with tannic acid, thus the modified gelatin of the first outer layer or sheath conveniently presents suitable gastroresistant properties, which allow the capsule housing to be disaggregated only in intestinal juice. In case the first outer layer is made from other suitable not gelatinous material, alike polyphenyl compounds, the gastroresistance can be achieved applying to the capsule housing a suitable coating composition, as known in the art, to produce stable capsules, resistant to the acid secretions of the stomach and dissolved in the alkaline fluid of the intestinal secretions. The gastroresistance control method is indicated in USP XXII, (page 1577-1578). This method is consisting of putting the capsules in artificial gastric juices for one hour, then in artificial intestinal juices and of measuring the time of disaggregation in this latter liquid.

Another more particularly embodiment of the unit dosage drug delivery system of this invention consists of extending the dissolution rate of the active drug substance over a wide range of time, by incorporation in the silicone resin of one or more release modifying substances. This is a particularly advantageous feature, as it allows the release rate to be modified as desired and to provide a suitable controlled dissolution rate of the active drug substance. Suitably pharmaceutical grade excipients, which produce an extended rate of dissolution, include hydrophobic release modifying substances, such as the following or mixture thereof : beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glyceryl stearate, ethyl oleate, arachids oil, cotton seed oil, rape seed oil, liquid paraffin, polyethylene glycol (from 400 to 20,000), mono-, di- and/or triglycerides such as Miglyols (trade mark), Labrafils (trade mark), Precirols (trade mark) and Gelucires (trade mark). The quantity of the release modifying substances, incorporated into the silicone resin, depends on their nature and on the required release properties. More particularly the level of the release modifying substances is further comprising of from 15 % to 60 %, preferably between 20 % and 55 % by weight of the silicone resin of the capsule filling. The release modifying substances may be incorporated in the silicone resin by admixing, dissolving, suspending,

agglomerating, homogeneizing or melting them together. The extended release control method is indicated in USP XXII (page 1580).

PRODUCTION PROCESS

The production process is conveniently carried out in air-conditioned areas to assure the proper conditioning (drying) of the multiple layers, sheaths or films of the capsule housing, the protection of the capsule filling to preserve low moisture content of active drug substances and their mixtures thereof. More particularly the temperature range in the areas is 15° C - 24° C (60° F - 75° F) and the humidity is 20 % - 40 %.

In the *capsule housing preparation department*, are individually weighed the solid elements of the multiple layers, sheaths or films, mixed with accurately metered and chilled (at about 8° C / 45° F) liquid elements. Then the resulting masses of each layer, sheath or film are individually transferred to separate melting tanks, where are melted, under stirring and vacuum (from 730 to 750 mm Hg) at about 90° C (200° F) of temperature. The operations are carried out simultaneously in conventional mixers, for example mixers of stainless steel or similar material. To the mass of the first outer hydrophilic layer or sheath conventional additives, including colouring agents, plasticizers, opacifiers and preserving agents and

antioxidants may be added. Usually for each mixing process it is necessary 25 minutes and for melting procedure about 2 hours. At this moment, a sample of the resulting mass of the first outer layer is taken and compared visually against a colour standard; if adjustments are required, more colorants are added. The masses of each layer, sheath or film are maintained in different mixers at a temperature of 57° C - 60° C (135° F - 140° F), before and during the capsulation process. The *materials preparation department* will have a weighing and mixing area equipped with the necessary equipment and facilities for the preparation of a variety of fill mixtures, that may be encapsulated. An initial blending of the capsule fill ingredients (basically active drug substance, silicone resin and other solids and liquids) is completed in suitable stainless steel, jacketed tanks and mixers. When the above step is completed, the masses are individually subjected to a milling or homogenizing process (homoloid mill, stone mill or hopper mill may be conveniently used as equipment), not to reduce the particle size, but to break up agglomerates of solids and to ensure that all ingredients are suitably wetted with the liquid carrier. In case of extended release preparation, the release modifying substances are admixed, dissolved, suspended, agglomerated or melted together to the above mixture at this stage. Then the resulting capsule fill is subjected to de-aeration to achieve uniform capsule fill weight and

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protection from the oxidation before and during capsulation. It is convenient sending samples of the mixture fill to the control laboratories for various tests, alike ingredients assays, homogeneity tests, moisture content and air entrapment. After quality approval, the capsule fill is transferred from the mixing tank to the fill tank, the container that will be used at the capsulation machine. In order to better describe the fundamental aspects of the instant invention, a schematic drawing of the same production process is presented in Figure 1; the mass of the first outer hydrophilic layer is fed by gravity to a spreader box and the flow of this mixture, on to rotating drum (1), cooled at 13° C - 15° C (56° F - 58° F) of temperature, is obtained by gravity or under pressure. The first outer layer or sheath, obtained with a controlled thickness, is fed over guide rolls and then down, between the injection wedge and the die rolls. On the same fashion, the second and the additional inner films or sheaths (made from silicone or silicone mixture), are individually obtained and coupled with the internal face of the first outer layer or sheath, by passing them between the wedge and the die rolls to obtain the capsule housing. In Figure 2 is presented an alternative method of capsulation process, where the second rotating drum (2) is replaced by a spreader box. The spreader box is installed on the top of the first rotating drum and deposits directly, by gravity or under pressure, the second hydrophobic sheath or film of

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the desired thickness on internal face of the outer layer or sheath. Any additional inner layer or sheath is then obtained and incorporated to the capsule housing as previously described. The capsule filling, to be capsulated, flows by gravity from the fill tank into a positive displacement pump and then, accurately metered by this pump, through the leads and the wedge, into the capsule housing (made from multiple coupled layers, sheaths or films), between the die rolls. In the bottom of the wedge, there are small orifices, lined up with die pockets of the die rolls. The capsule is about half sealed, when the pumped material forces the various films into the die pockets, where the capsules are filled, shaped, and hermetically sealed and cut from the ribbons. The sealing of the capsule is obtained by mechanical pressure on the die rolls and the heating (37°C - 40° C) of the capsule housing by the wedge; thus the capsules can be preliminary dried or spread directly on trays and placed in drying tunnels. The capsules are air-conditioned in area having 20 % to 30 % of relative humidity and 20° C - 24° C (70° F - 75° F) of temperature. At the end of the manufacturing process, the soft capsules of the invention are sent to the inspection department and held until released by the quality controls. Control tests specifically applicable are : seal thickness determinations, moisture tests, fragility or rupture tests, and determination of freezing and high temperature effects. The determination of dosage weight

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for the content of the drug substance shall be also controlled as indicated in USP XXII. They may be stored for long periods without any sign of degradation or decomposition. Immediately before or after any period of storage, when necessary, the soft capsules can be sent to a gastroresistance department and processed, with methods as described before.

The difference of the soft gelatin capsules of the prior art and of the unit dosage drug delivery system of this invention is further evidenced by the illustration of Figure 3, showing cross section diagrams of the claimed product.

The new soft capsules of invention have excellent pharmaceutical properties and acceptability. They are chemically and physically stable and do not develop significant pH variation during storage. It is surprising that the new pharmaceutical soft capsules of this invention, manufactured from coupled multiple layers, sheaths or films, incorporating a mixture of active drug substances and silicone resin, are considerably more stable and present an improved protection from adversely affecting agents, alike atmosphere, moisture and oxidation and substantially prevent the diffusion of the residual water contained from the capsule housing to sensitive active drug substance incorporated in the capsule filling.

In order to better illustrate the instant invention, the following examples are reported, that in any case may not be considered limitative.

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EXAMPLE 1 : Preparation of 9,100 soft capsules of cyclosporin 25 mg (2 oval)

Each soft capsule containing :

CAPSULE FILLING

- cyclosporin	25.000	mg
- silicone resin (viscosity 100 cSt)	50.000	mg
- absolute ethanol	25.000	mg

Total weight of the content 100.000 mg

CAPSULE HOUSING

First outer layer :

- gelatin	49.230	mg
- glycerol	26.263	mg

Second inner layer :

- silicone (viscosity 125 cSt)	3.720	mg
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Total weight of the capsule housing 79.213 mg

Capsule housing/first outer layer

448 g of gelatin, 239 g of glycerol and 494 g of water are mixed. This mixture is melted under vacuum (730-750 mm Hg) and stirring in a stainless steel tank at a temperature between 75° C and 80° C, until the melting is absolutely complete. The opaque mass, thus obtained, is then used for making the first outer layer ribbon (wet thickness about 0.76 mm), in the manner described before (Figure 2/Drum 1).

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Capsule housing/second inner layer

33.85 g of silicone, having an intrinsic viscosity of about 125 cSt, are placed in a spreader box installed on the top of the rotating drum 1, that deposits continuously on the internal surface of the first outer gelatin ribbon, an uniform film, thickness about 50 μ m (Figure 2).

Capsule filling

455 g of silicone resin, having a viscosity of 100 cSt, are mixed with 227.5 g of cyclosporin (100 % assay) and 227.5 g of absolute ethanol, until complete homogeneity. The suspension thus obtained is loaded, under constant stirring, into the fill tank of the fill pump of the machine for the production of soft capsules (Figure 2). The wet soft capsules are then dried and stabilized according to conventional methods on trays, placed in drying tunnels (72 hours at 20° C - 25° C). 7,470 soft capsules pass the visual inspection and the control tests. Yield : 82.08%.

EXAMPLE 2: Preparation of 16,250 soft capsules of captopril 25 mg (2 round).

Each soft capsule containing :

CAPSULE FILLING

- captopril	25.000	mg
- silicone resin (viscosity 150 cSt)	75.000	mg

Total weight of the content	100.000	mg

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CAPSULE HOUSING

First outer layer :

- gelatin	49.280	mg
- modified sorbitol solution 45 %	26.320	mg
- titanium dioxide E 171	0.798	mg
- iron oxide red E 172	0.020	mg

Second inner layer :

- silicone (viscosity 200 cSt)	4.807	mg
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Total weight of the capsule housing	81.225	mg
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Capsule housing/first outer layer

800.8 g of gelatin, 427.7 g of modified sorbitol solution 45 % (in water), 715.0 g of water, 12.97 g of titanium dioxide (E 171), 0.325 g of iron oxide red (E 172) are conveniently mixed, under vacuum (730 - 750 mm Hg) in a stainless steel tank at a temperature between 75° C and 80° C, until the melting is homogeneous and complete. The resulting pink mass is then used for preparing the first outer layer ribbon (wet thickness about 0.82 mm) on the fashion already described.

Capsule housing/second inner layer

78.11 g of silicone, viscosity about 200 cSt, are introduced in a spreader box, placed on the top of the rotating drum 1. In this manner, in the internal face of the first outer layer is deposited an uniform film with a thickness of about 65 µm.

Capsule filling

1,219.0 g of silicone resin, having a viscosity of 150 cSt, are added to 406.25 g of captopril (adjusted to 100 % titre) in a suitable mixer and the suspension is loaded into the fill tank of the fill pump of the capsule machine for the production of soft capsules (Figure 2). The resulting wet soft capsules are dried and stabilized according to conventional methods on trays, placed in drying tunnels (60 hours to 28° C - 30° C). 13,100 soft capsules pass the visual inspection and the control tests. Yield : 80.6 %.

EXAMPLE 3: Preparation of 32,500 soft capsules of lysozyme hydrochloride 250 mg (20 oblong)

Each soft capsule containing :

CAPSULE FILLING

- lysozyme hydrochloride	250.000	mg
- silicone resin (viscosity 125 cSt)	850.000	mg

Total weight of the content	1100.000	mg
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CAPSULE HOUSING

First outer layer :

- gelatin	261.154	mg
- glycerol	139.384	mg
- titanium dioxide E 171	9.230	mg

Second inner layer :

- silicone (viscosity 250 cSt)	36.077	mg
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Total weight of the capsule housing	445.845	mg
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Capsule housing/first outer layer

8.49 Kg of gelatin, 4.53 Kg of glycerol, 0.3 Kg of titanium dioxide (E 171) and 9.38 Kg of water are mixed thoroughly and the mixture is melted in a stainless steel tank, under vacuum and constant stirring, at a temperature between 75° C and 80° C. When the melting is completed, the mass is used for preparing the first outer layer ribbon on the fashion already described, having a thickness of about 0.96 mm.

Capsule housing/second inner layer

1,172.0 g of silicone, having an intrinsic viscosity of about 250 cSt are placed in a spreader box, installed on the top of the rotating drum 1, that dispensed continuously on the internal surface of the first outer gelatin ribbon an uniform film, having a thickness of about 60 µm (Figure 2).

Capsule filling

27.625 Kg of silicone resin, having a viscosity of 125 cSt, are mixed with 8.125 Kg of lysozyme hydrochloride (100 % assay) and the obtained paste is loaded, under pressure into the fill tank of the fill pump of the machine for the production of the soft capsules (Figure 2). The wet soft capsules are then dried and stabilized according to

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conventional methods on trays, placed in drying tunnels (80 hours at about 25° C). 24,520 soft capsules pass the visual inspection and the control tests. Yield : 75.44 %.

EXAMPLE 4: Preparation of 24,000 gastroresistant soft capsules of lansoprazole 30 mg (2 oval).

Each gastroresistant soft capsule containing :

CAPSULE FILLING

- lansoprazole	30.000	mg
- silicone resin (viscosity 250 cSt)	69.250	mg
- sodium laurylsarcosinate	0.750	mg

Total weight of the content	100.000	mg

CAPSULE HOUSING

First outer layer :

- gelatin	49.250	mg
- modified sorbitol solution 45%	12.916	mg
- glycerol	13.333	mg
- titanium dioxide E 171	0.351	mg
- Ponceau red (FD & C Red n°1/E 124)	0.418	mg
- quinoline yellow (E 104)	0.025	mg

Second inner layer :

- silicone (viscosity 300 cSt)	9.121	mg

Total weight of the capsule housing	85.414	mg

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Capsule housing/first outer layer

1,182.0 g of gelatin, 310.0 g of modified sorbitol solution 45 % (in water), 320.0 g of glycerol, 1,200.0 g of water, 8.43 g of titanium dioxide (E 171), 10.03 g of Ponceau red (FD & C Red. n°/E 124), 0.6 g of quinoline yellow (E 104) are conveniently mixed, under stirring and vacuum (730 - 750 mm Hg), in a stainless steel tank at a temperature between 75° C - 80° C, until the melting is complete. The red gelatin mass is utilized to obtain the first outer layer ribbon (wet thickness about 0.75 mm) by a process as previously described.

Capsule housing/second inner layer

218.91 g of silicone, having a viscosity of about 300 cSt, flow by gravity in a spreader box on the top of the rotating drum 1, that continuously deposits an uniform film, with a thickness of about 80 µm, in the internal face of the first outer layer.

Capsule filling

1,662.0 g of silicone resin, with a viscosity of 250 cSt, are mixed with 720.0 g of lansoprazole (100 % assay) and 18 g of sodium laurylsarcosinate. The resulting suspension is placed in the fill tank of the fill pump of the capsule machine for the production of the soft capsules. The soft capsules are manufactured in the usual manner as described in Figures 1 and 2. The resulting wet soft capsules are dried and stabilized, according to conventional methods on trays, placed in drying tunnels

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(72 hours at 20° C - 25° C). 19,407 soft capsules pass the visual inspection and the control tests. Yield : 80.86 %.

Gastroresistance process

The above soft capsules are employed for the preparation of gastroresistant capsules by proceeding on the following fashion : a conventional quantity of capsules (about 10,000) are introduced in a turbine (or rotating pan). By means of a tube connected with a tank, containing formaldehyde dispersion in acetone in the ratio of 1:60 (formaldehyde at 30 % potency in acetone), the soft capsules are sprayed by using 503.3 g of this dispersion. The formaldehyde is immediately fixed by the first outer hydrophilic layer and the acetone is simultaneously evacuated by a suction devices provided inside the turbine (or rotating pan). The soft capsules are packed individually in blisters.

The gastroresistance of 2 hours (measured according to USP XXII pages 1577-1578) was reached 4 days after treatment, being made as a function of the ageing of the capsules. The time of opening of gastroresistant soft capsules in the artificial intestinal juice, for an ageing of 2 months to one year, is practically constant at 200 seconds.

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EXAMPLE 5: Preparation of 26,000 extended release soft capsules of nicorandil 45 mg (2 oval).

Each extended release soft capsule containing :

CAPSULE FILLING

- nicorandil	45.000	mg
- silicone resin (viscosity 300 cSt)	55.000	mg

Total weight of the content	100.000	mg

CAPSULE HOUSING

First outer layer :

- gelatin	49.269	mg
- modified sorbitol solution 45 %	26.307	mg
- titanium dioxide E 171	0.800	mg
- iron oxide red E 172	0.040	mg

Second inner layer :

- silicone (viscosity 100 cSt)	6.322	mg
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Third inner layer :

- silicone elastomer (with pores)	4.353	mg
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Total weight of the capsule housing	87.091	mg

Capsule housing/first outer layer

1,281.0 g of gelatin, 684.0 g of modified sorbitol solution 45 % (in water), 20.8 g of titanium dioxide (E 171), 1.04 g of iron oxide red (E 172) and 900 g of water are conveniently mixed, under vacuum and stirring, in a

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stainless steel tank at a temperature of 75° C - 80° C. The pink gelatin mass is utilized to obtain the first outer layer ribbon (wet thickness about 0.76 mm), by a process as previously described.

Capsule housing/second inner layer

164.37 g of silicone, having a viscosity of about 100 cSt, are introduced in a spreader box, placed on the top of the rotating drum 1. In this manner on the internal face of the first outer layer is deposited an uniform film with a thickness of about 55 µm (Figure 2).

Capsule housing/third inner layer

A suitable ribbon from silicone elastomer (thickness about 30 µm, melting point of 39° C - 40° C, pore distribution of 50 pores/mm², pore size about 50 µm) is automatically released from a third rotating drum and coupled on the internal face of the second inner layer (Figure 1) .

Capsule filling

1.43 Kg of silicone resin, having a viscosity of 300 cSt, are mixed with 1.170 Kg of nicorandil (100 % assay) and the resulting viscous suspension is loaded, under pressure, in the fill tank of the fill pump of the machine for the production of the soft capsules (Figure 1). The wet soft capsules are then dried and stabilized according to conventional method on trays, placed in drying tunnels (72 hours at 20° C - 25° C). 18,970 soft capsules pass the visual inspection and the control tests. Yield : 72.96 %.

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EXAMPLE 6 : Preparation of 30,500 extended release soft capsules of nicorandil 30 mg (2 oval).

Each extended release soft capsule containing :

CAPSULE FILLING

- nicorandil	30.000	mg
- silicone resin (viscosity 800 cSt)	45.000	mg
- white wax	25.000	mg

Total weight of the content	100.000	mg
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CAPSULE HOUSING

First outer layer :

- gelatin	49.246	mg
- modified sorbitol solution 45 %	26.307	mg
- titanium dioxide E 171	0.720	mg
- iron oxide red E 172	0.120	mg

Second inner layer :

- silicone (viscosity 150 cSt)	6.885	mg
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Total weight of the capsule housing	83.278	mg
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Capsule housing/first outer layer

1,502.0 g of gelatin, 802.36 g of modified sorbitol solution 45 % (in water), 21.96 g of titanium dioxide (E 171), 3.66 g of iron oxide red (E 172) and 1,055.0 g of water are mixed. This mixture is melted, under vacuum (730 - 750 mm Hg) and stirring, in a stainless steel tank at a temperature

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between 75° C and 80° C until the melting is absolutely complete. The red-brown coloured gelatin mass is utilized to make the first outer layer ribbon (wet thickness of about 0.76 mm) on the fashion described before (Figure 2).

Capsule housing/second inner layer

209.99 g of silicone, having a viscosity of about 150 cSt, are introduced in a spreader box, installed on the top of the rotating drum 1, that deposits continuously, on the internal surface of the first outer gelatin ribbon, an uniform film with a thickness of about 60 µm (Figure 2).

Capsule filling

1.372 Kg of liquid silicone resin, having a viscosity of 800 cSt, are mixed with 915.0 g of nicorandil (100 % assay). 762.5 g of white wax, previously melted at about 75° C are added to the mixture, under stirring at 25° C for about 5 minutes, until obtaining an uniform support. The resulting mass is loaded, under constant stirring, into the fill tank of the fill pump of the machine for the production of soft capsules. In this manner is made a delivery system that assures the extended release of the active drug substance, due to the slow liberation from the support. The wet soft capsules are then dried and stabilized according to conventional methods on trays, placed in drying tunnels (72 hours at 20° C - 25° C). 18,950 soft capsules pass the visual inspection and the control tests. Yield : 62.13 %.

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Extended release test of the soft capsules of Example 6

The test is carried out according by USP XXII, page 1581, "Extended Release Article".

The obtained results are indicated in the following table :

hours	% of nicorandil released
2 h.	25 %
6 h.	42 %
12 h.	70 %

EXAMPLE 7 : Preparation of 25,000 extended release soft capsules of sodium bicarbonate 500 mg (20 oblong).

Each extended release soft capsule containing :

CAPSULE FILLING

- sodium bicarbonate	500.0	mg
- silicone resin (viscosity 600 cSt)	470.0	mg
- white wax	130.0	mg

Total weight of the content	1100.0	mg
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CAPSULE HOUSING

First outer layer :

- gelatin	261.154	mg
- glycerol	139.384	mg
- titanium dioxide E 171	9.230	mg

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Second inner layer :

- silicone (viscosity 250 cSt) 44.984 mg

Total weight of the capsule housing 454.752 mg

Capsule housing/first outer layer

6.53 Kg of gelatin, 3.48 Kg of glycerol, 7.21 Kg of water and 0.23 Kg of titanium dioxide (E 171) are mixed thoroughly and the mixture is melted in a stainless steel tank, under vacuum and constant stirring, at a temperature between 75° C and 80° C. When the melting is completed, the mass is used for preparing the first outer layer ribbon on the fashion already described, having a thickness of about 0.96 mm.

Capsule housing/second inner layer

1,124.0 g of silicone, having an intrinsic viscosity of about 250 cSt, are placed in a spreader box, installed on the top of the rotating drum 1, that dispenses continuously, on the internal surface of the first outer gelatin ribbon, an uniform film, having a thickness of about 75 µm (Figure 2).

Capsule filling

11.75 Kg of silicone resin, having a viscosity of 600 cSt, are mixed with 12.5 Kg of sodium bicarbonate. 3.25 Kg of white wax, previously melted at about 75° C are added to the mixture under stirring at 25° C for about 5 minutes, until obtaining an uniform support. The resulting mass is loaded, under constant stirring, into the fill tank of the

fill pump of the machine for the production of the soft capsules. The wet soft capsules are then dried and stabilized, according to conventional methods on trays, placed in drying tunnels (72 hours at 20° C - 25° C). 16,825 soft capsules pass the visual inspection and the control test. Yield : 67.3 %.

Extended release test of the soft capsules of Example 7

The obtained delivery system permits the extended release of the antacid because of the slow liberation of sodium bicarbonate. The test is carried out according USP XXII, page 1581, "Extended Release Article".

The obtained results are indicated in the following table :

hours	% of NaHCO ₃ released
1 h.	28 %
3 h.	51 %
5 h.	75 %

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention shall be limited solely by the scope of the following claims including equivalents thereof.

WHAT IS CLAIMED IS :

- 1) A unit dosage drug delivery system which comprises :
 - a) a multiple layers capsule housing, consisting of at least two or more coupled layers, sheaths or films from different materials, the first outer layer or sheath with hydrophilic character and the inner sheaths or films with hydrophobic character.
 - b) a capsule filling, embodying one or more active drug substances, with conventional or extended drug release properties, with a remarkable hydrophobic character.
- 2) The unit dosage drug delivery system, as defined in Claim 1, said multiple layers capsule housing, comprising :
 - A₁) a first outer hydrophilic layer, consisting either of a mixture of gelatin, glycerin and/or modified sorbitol solution, water or alternatively of other suitable compounds, alike polyphenyl compounds.
 - A₂) a second inner hydrophobic film or sheath from silicone, silicone mixture or other pharmaceutically acceptable silicone polymers.
 - A₃) an optional inner third or additional films or sheaths, made from silicone polymers or waxes or alternatively from jaluronic acid polymers.
- 3) The unit dosage drug delivery system, as defined in Claim 1, said capsule filling, confined within the capsule housing, containing:
 - B₁) one or more active drug substances which, are admixed,

dissolved, suspended or agglomerated in an hydrophobic support.

B₂) silicone resin having a viscosity in the range of from 100 to 1,100 cSt and specific gravity in the range of from 0.96 to 1.02.

B₃) optional components particularly sodium lauryl-sarcosinate in the range from 0.1 % to 2.0 % and absolute ethanol in the range from 1.0 % to 30.0 %, preferably from 10.0 % to 25.0 % of the capsule filling.

B₄) optional release modifying substances, providing an extended release of the active medicinal drug, said modifying substances comprising : beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glyceryl stearate, ethyl oleate, arachids oil, cotton seed oil, rape seed oil, liquid paraffin, polyethylene glycol from 400 to 20,000.

4) The unit dosage drug delivery system, as defined in Claim 1, having size, shape and colour of a conventional capsule for oral, rectal or vaginal administration.

5) The unit dosage drug delivery system, as defined in Claim 1-a), wherein the capsule housing, has conventional or enteric release dissolution.

6) The unit dosage drug delivery system, as defined in Claim 2-A₁), wherein the first outer hydrophilic layer of the capsule housing, presents a thickness at the wet state preferably comprised between 0.50 mm and 1 mm.

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7) The unit dosage drug delivery system, as defined in Claim 2-A₂), wherein a second inner hydrophobic film or sheath of the capsule housing is made from silicone, having a low-medium viscosity comprised between 10 and 200,000 cSt.

8) The unit dosage drug delivery system, as defined in Claim 2-A₂), wherein the second inner hydrophobic film or sheath of the capsule housing presents a thickness comprised between 0.1 and 100 μm , preferably between 50 and 80 μm .

9) The unit dosage drug delivery system, as defined in Claim 2-A₃), having an optional inner third or multiple films or sheaths of the capsule housing, with a thickness comprised between 0.1 and 100 μm , preferably between 5 and 50 μm and a melting range of about 39° C - 40° C.

10) The unit dosage drug delivery system, as defined in Claim 2-A₃), having a third inner hydrophobic film or sheath of the capsule housing optionally covered with pores of suitable size, preferably comprised between 10 and 100 μm and pore distribution from 2,500 to 25 pores/ mm^2 , in order to achieve a retarded diffusion of the active drug substance.

11) The unit dosage drug delivery system, as defined in Claim 2-A₂), wherein the second inner hydrophobic sheath or film of the capsule housing has an intrinsic viscosity lower than that of the third inner film or sheath.

12) The unit dosage drug delivery system, as defined in

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Claim 2-A₁), wherein the first outer hydrophilic layer represents from 83.33 % to 99.96 % by weight of the entire capsule housing, preferably between 90 % and 98 %.

13) The unit dosage drug delivery system, as defined in Claim 2-A₂), wherein the sum of the second inner hydrophobic film or sheath and of the optional inner third or multiple films or sheaths, is further comprising of from 0.04 % to 16.67 % by weight of the entire capsule housing, preferably between 2 % and 10 %.

14) The unit dosage drug delivery system, as defined in Claim 3, wherein the capsule filling contains one or more active drug substances, selected among the groups of oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antisecretories, antacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, diuretic agents, antineoplastic agents, antiviral nucleosides agents, antifungal agents, antiparkinson agents, antiepileptic agents, analgesics, non steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their organic and inorganic salts, liophylized yeasts and vitamins.

15) The unit dosage drug delivery system, as defined in Claim 3, wherein the capsule filling contains one or more pharmaceutical active drug substances, in the range of from 0.0001 % to 45 % by weight.

16) The unit dosage drug delivery system, as defined in Claim 3-B₃), wherein the release modifying substances are

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further comprising of from 15 % to 60 %, preferably between 20 % and 55 % by weight of the silicone resin of the capsule filling.

17) The unit dosage drug delivery system, as defined in Claim 2, wherein the multiple layers capsule housing presents an enteric release coating, obtained by conventional gastroenteric coating methods, preferably by immersion in a solution of formaldehyde dispersed in acetone in a ratio 1 : 60.

18) The unit dosage drug delivery system, as defined in Claim 2-A₁), wherein the first outer layer of the capsule housing is made from polyphenyl compounds, wherein the gastroenteric release coating is obtained by applying a suitable conventional coating composition.

19) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains attenuated vaccines, preferably cholera vaccine.

20) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains typhoid vaccine.

21) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains live vaccines, preferably poliomyelitis vaccine.

22) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains polypeptides, preferably calcitonins.

23) The unit dosage drug delivery system, as defined in

Claim 14, wherein the capsule filling contains erythropoietin.

24) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains insulin.

25) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains polypeptides with immunosuppressive activity, preferably cyclosporins

26) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains vaccines for mammals, preferably oral vaccines.

27) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains enzymes, preferably lysozyme.

28) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains digestive enzymes, like trypsin.

29) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains carboxypeptidase.

30) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains growth regulator, preferably interleukin 1.

31) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains prostaglandins, preferably prostaglandin A₁.

32) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains

prostaglandin E₂.

33) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains methyl prostaglandin F_{2α}.

34) The unit dosage drug delivery system, as defined in claim 14, wherein the capsule filling contains prostaciclins, preferably prostaglandin I₂.

35) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains misoprostol.

36) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains tromboxanes.

37) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains cholesterol lowering agents, preferably eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA).

38) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains H⁺/K⁺ ATPase inhibitors, preferably omeprazole.

39) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains lansoprazole.

40) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains H₂-antagonists, preferably ranitidine or its salts.

41) The unit dosage drug delivery system, as defined in

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Claim 14, wherein the capsule filling contains famotidine.

42) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiacids agents, preferably sodium bicarbonate.

43) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiallergic agents.

44) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiasthmatic agents, preferably cetirizine and its salts.

45) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains bamiphylline.

46) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains ACE inhibitors, preferably captopril.

47) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains enalapril.

48) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antineoplastic agents, preferably etoposide.

49) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains estramustine phosphate sodium.

50) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiviral nucleosides agents, preferably acyclovir.

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51) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antifungal agents, preferably itraconazole.

52) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiparkinson agents, preferably selegiline and its salts.

53) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains antiepileptic agents, preferably lamotrigine.

54) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains anti-inflammatory agents, preferably aspirin.

55) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains piroxicam.

56) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains ketorolac.

57) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains calcium blocking agents, preferably nifedipine.

58) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains the calcium antagonist amlodipine.

59) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains diltiazem and its salts.

60) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains

vasodilators agents, preferably nicorandil.

61) The unit dosage drug delivery system, as defined in Claim 14, wherein the capsule filling contains liophylized yeasts, preferably lactobacillus bifidus and lactobacillus bulgaricus.

62) The unit dosage drug delivery system, as defined in Claims from 1 to 61, particularly suitable and convenient for delivering active drug substances, selected among the groups of oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antisecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, diuretic agents, antineoplastic agents, antiviral nucleosides agents, antifungal agents, antiparkinson agents, antiepileptic agents, analgesics, non steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their organic and inorganic salts, liophylized yeasts and vitamins, sensitive to moisture, oxidation or easily degradable from the atmosphere.

63) The unit dosage drug delivery system, as defined in Claims from 1 to 61, which advantageously prevent the diffusion of the water soluble active drug substances or of their pharmaceutically acceptable salts, selected among the groups of oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antisecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, diuretic agents, antineoplastic

agents, antiviral nucleosides agents, antifungal agents, antiparkinson agents, antiepileptic agents, analgesics, non steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their organic and inorganic salts, liophylized yeasts and vitamins, from the capsule filling to the first outer hydrophilic layer of the capsule housing.

64) A method for preparing the unit dosage drug delivery system, which comprises the steps of :

1/ providing a capsule housing comprising the following ingredients :

1/(a) a first outer hydrophilic layer, consisting either of a mixture of gelatin, glycerin and/or modified sorbitol solution, water or alternatively of other suitable compounds, alike polyphenyl compounds.

1/(b) a second inner hydrophobic film or sheath from silicone, silicone mixture or other pharmaceutically acceptable silicone polymers.

1/(c) an optional inner third or additional films or sheaths, made from silicone polymers or waxes or alternatively from jaluronic acid polymers.

2/ providing a capsule filling, comprising the following ingredients :

2/(a) one or more active drug substances which are admixed, dissolved, suspended or agglomerated in an hydrophobic support.

2/(b) silicone resin having a viscosity in the range of from

100 to 1,100 cSt and specific gravity in the range of from 0.96 to 1.02.

2/(c) optional components particularly sodium lauryl-sarcosinate in the range from 0.1 % to 2.0 % and absolute ethanol in the range from 1.0 % to 30.0 %, preferably from 10.0 % to 25.0 % of the capsule filling.

2/(d) optional release modifying substances, providing an extended release of the active medicinal drug, said modifying substances comprising : beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glyceryl stearate, ethyl oleate, arachids oil, cotton seed oil, rape seed oil, liquid paraffin, polyethylene glycol from 400 to 20,000.

65) The method, according to Claim 64, wherein the capsule housing has conventional or enteric release dissolution.

66) The method, according to Claim 64, wherein the first outer hydrophilic layer of the capsule housing, presents a thickness at the wet state preferably comprised between 0.50 mm and 1 mm.

67) The method, according to Claim 64, wherein a second hydrophobic inner film or sheath of the capsule housing is made from silicone, having a low-medium viscosity comprised between 10 and 200,000 cSt.

68) The method according to Claim 64, wherein the second inner hydrophobic film or sheath of the capsule housing

presents a thickness comprised between 0.1 and 100 μm , preferably between 50 and 80 μm .

69) The method, according to Claim 64, having an optional inner third or multiple films or sheaths of the capsule housing, with a thickness comprised between 0.1 and 100 μm , preferably between 5 and 50 μm and a melting range of about 39° C - 40° C.

70) The method, according in Claim 64, wherein the third film or sheath of the capsule housing is optionally covered with pores of suitable size, preferably comprised between 10 and 100 μm and pore distribution from 2,500 to 25 pores/ mm^2 , in order to achieve a retarded diffusion of the drug substance.

71) The method, according to Claim 64, wherein the second inner hydrophobic sheath or film of the capsule housing has an intrinsic viscosity lower than that of the optional third inner film or sheath.

72) The method, according to Claim 64, wherein the first hydrophilic outer layer represents from 83.33 % to 99.96 % by weight of the entire capsule housing, preferably between 90 % and 98 %.

73) The method, according to Claim 64, wherein the sum of the second inner hydrophobic film or sheath and of the optional inner third or multiple film or sheath, is further comprising from 0.04 % to 16.67 % by weight of the entire capsule housing, preferably between 2 % and 10 %.

74) The method, according to Claim 64, wherein the

capsule filling contains one or more active drug substances, selected among the groups of oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antiseecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, diuretic agents, antineoplastic agents, antiviral nucleosides agents, antifungal agents, antiparkinson agents, antiepileptic agents, analgesics, non steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their organic and inorganic salts, liophylized yeasts and vitamins.

75) The method, according to Claim 64, wherein the capsule filling contains one or more pharmaceutical drug substances, in the range of from 0.0001 % to 45 % by weight.

76) The method, according to Claim 64, wherein the capsule filling contains the release modifying substances further comprising of from 15 % to 60 %, preferably between 20 % to 55 % by weight of the silicon resin, excluding the active drug substance.

77) The method, according to Claim 64, wherein the multiple layers capsule housing presents an enteric release coating, obtained by conventional gastroenteric coating methods, preferably by immersion in a solution of formaldehyde dispersed in acetone in a ratio 1 : 60.

78) The method, according to Claim 64, wherein the first outer layer of the capsule housing is made from polyphenyl

compounds, wherein the gastroenteric release coating is obtained by applying a suitable conventional coating composition.

79) A medicated composition, which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a unit dosage drug delivery system containing :

1/ a capsule housing comprising :

1/(a) a first outer hydrophilic layer, consisting either of a mixture of gelatin, glycerin and/or modified sorbitol solution, water or alternatively of other suitable compounds, alike polyphenyl compounds.

1/(b) a second inner hydrophobic film or sheath from silicone, silicone mixture or other pharmaceutically acceptable silicone polymers.

1/(c) an optional inner third or additional films or sheaths, made from silicone polymers or waxes or alternatively from jaluronic acid polymers.

2/ a capsule filling, comprising :

2/(a) one or more active drug substances which are admixed, dissolved, suspended or agglomerated in an hydrophobic support.

2/(b) silicone resin having a viscosity in the range of from 100 to 1,100 cSt and specific gravity in the range of from 0.96 to 1.02.

2/(c) optional components particularly sodium lauryl-sarcosinate in the range from 0.1 % to 2.0 % and absolute

ethanol in the range from 1.0 % to 30.0 %, preferably from 10.0 % to 25.0 % of the capsule filling.

2/(d) optional release modifying substances, providing an extended release of the active medicinal drug, said modifying substances comprising : beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glyceryl stearate, ethyl oleate, arachids oil, cotton seed oil, rape seed oil, liquid paraffin, polyethylene glycol from 400 to 20,000.

80) The medicated composition, as defined in Claim 79, adopted for oral, rectal or vaginal administration.

81) The medicated composition, as defined in Claim 79, wherein the active drug substances are advantageously protected from atmosphere, from oxidation, from moisture-induced hydrolytic or degradation processes.

82) The medicated composition, as defined in Claim 79, wherein the total moisture of the capsule filling content is less than 1 %.

83) The medicated composition, as defined in Claim 79, wherein the active drug substance is conveniently protected from moisture, oxidation and atmospheric degradation processes.

84) The medicated composition, as defined in Claim 79, wherein the diffusion of the active drug substance, from the capsule filling to the hydrophilic first outer layer of the capsule housing, is advantageously prevented by the

hydrophobic second inner layer.

85) The medicated composition, as defined in Claim 79, wherein the possible unpleasant taste or odor of the active drug substance is suitably masked, improving the administration compliance.

86) The medicated composition, as defined in Claim 79, adopted to extend the delivery of the active drug substance thereof, as to maintain a therapeutically plasma level thereof for a desired interval.

87) The medicated composition, as defined in Claim 79, for eliciting a therapeutic response in a mammalian organism in need of such treatment, comprising administering to such organism a therapeutically effective amount of the unit dosage drug delivery system.

88) A pharmaceutical product in unit dosage form which comprises:

a) a multiple layer capsule or housing having two or more layers said layers being of different materials, wherein the outer layer possesses a hydrophilic character and the inner layer possesses a hydrophobic character, and wherein there is in contact with the inner layer.

b) one or more drug substances having a hydrophobic character.

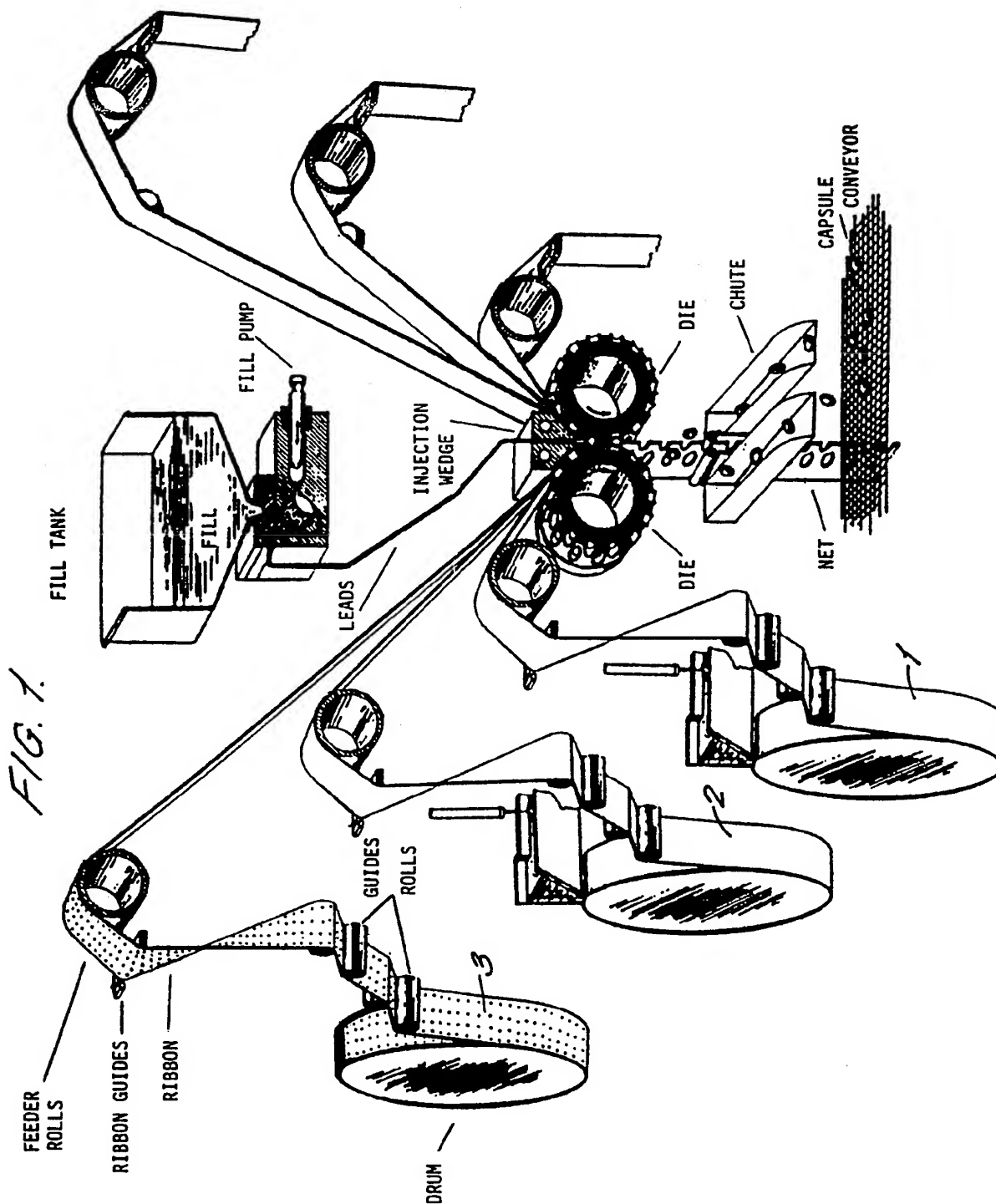
89) A drug delivery system constructed arranged and adapted substantially as herein before described with reference to any one of the accompanying examples.

90) A drug delivery system constructed arranged and

adapted substantially as herein before described with reference to and or illustrated in Figure 3.

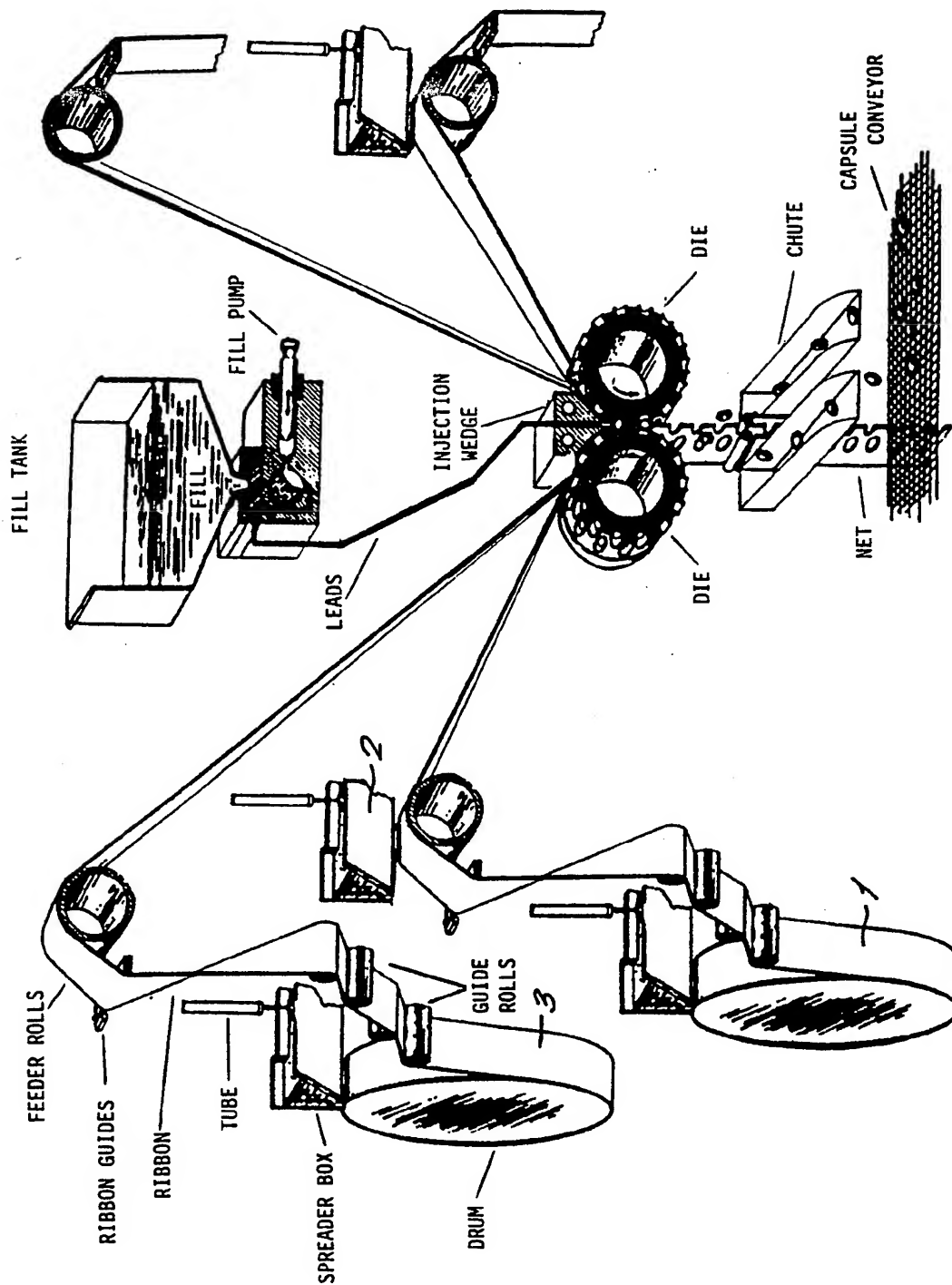
91) A method of preparing drug delivery system substantially as herein before described with reference to and as illustrated in any one of accompanying Figure 1 or 2.

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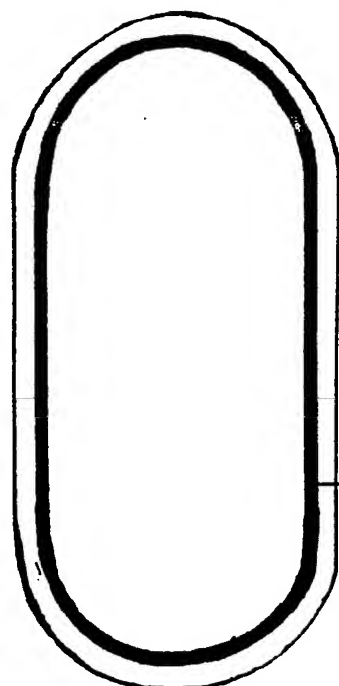


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FIG. 2.



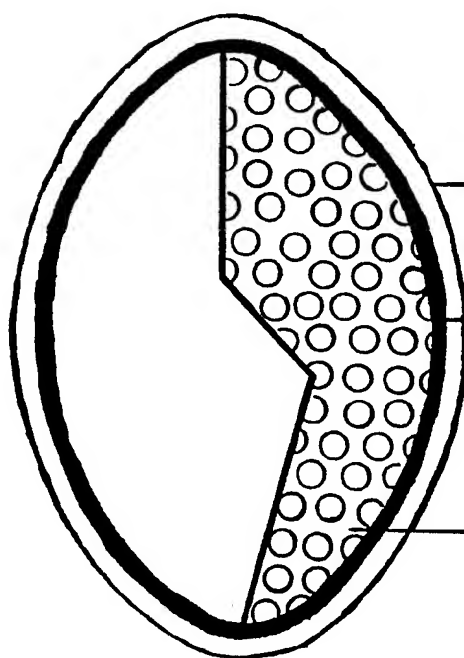
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FIG. 3.



First outer hydrophilic layer

Second inner hydrophobic film

20 OBLONG



First outer hydrophilic layer

Second inner hydrophobic film

Third inner hydrophobic sheath
with pores

2 OVAL

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/02488

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 013 no. 562 (C-665) ,13 December 1989 & JP,A,01 232963 (ARIMENTO KOGYO KK) 18 September 1989, see abstract -----	

☐ Further documents are listed in the continuation of box C.

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(21) International Application Number: PCT/SE95/00816 (22) International Filing Date: 5 July 1995 (05.07.95) (30) Priority Data: PCT/SE94/00679 8 July 1994 (08.07.94) WO (34) Countries for which the regional or international application was filed: SE et al. (60) Parent Application or Grant (63) Related by Continuation US 08/313,208 (CIP) Filed on 8 July 1994 (08.07.94) (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BENGTTSSON, Siv, Inga [SE/SE]; Klintens väg 13, S-414 76 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: NEW ORAL PHARMACEUTICAL FORMULATION CONTAINING MAGNESIUM SALT OF OMEPRAZOLE		
(57) Abstract <p>A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole coated with one or more enteric coating layers, a method for the manufacture of such a formulation, the use of such a formulation in medicine and a blister package containing the new formulation.</p>		

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NEW ORAL PHARMACEUTICAL FORMULATION CONTAINING MAGNESIUM
SALT OF OMEPRAZOLE

Field of the invention.

5 The present invention is related to a new pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, to a method for the manufacture of such a formulation, and to the use of such a formulation in medicine.

10 Background of the invention.

The compound known under the generic name omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is described i.a. in EP-A 0 005 129.

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Omeprazole is useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, said substances may be used for prevention and treatment of gastric acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole may
20 be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding,
25 pre- and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Further, omeprazole may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

Omeprazole is susceptible to degradation/transformation in acidic and neutral media. The half-life of degradation of omeprazole in water solutions at pH-values less than three is shorter than ten minutes. Omeprazole may be stabilized in mixtures with alkaline compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of omeprazole can occur.

A pharmaceutical oral dosage form of omeprazole may well be protected from contact with acidic gastric juice by an enteric coating. In US-A 4,786,505 an enteric coated omeprazole preparation is described. Said omeprazole preparation contains an alkaline core comprising omeprazole, a subcoating and an enteric coating.

The hard gelatine capsules containing an enteric coated pellet formulation of omeprazole marketed by the Applicant today, are not suitable for press-through blister packages. Thus, there has been a demand for development of new enteric coated preparations of omeprazole with good chemical stability as well as improved mechanical stability making it possible to produce well functioning and patient-friendly packages.

Certain salts of omeprazole including alkaline salts of omeprazole are described in EP-A 0 124 495. In said patent specification the requirements and importance regarding storage stability of omeprazole for incorporation in pharmaceutical preparations are emphasized.

There is however, a demand for the development of new enteric preparations of omeprazole with enhanced stability and for environmental aspects there is also a strong desire for the use of water based processes in production of pharmaceutical products.

5

The isolation and purification in full manufacturing scale of the magnesium omeprazole salts described in EP-A 0 124 495 presents one major problem in that the magnesium omeprazole salt particles are very fragile making pharmaceutical manufacturing processes utilising this product less attractive in full scale production. Manufacturing of magnesium omeprazole without a separate crystallisation step gives a product which is less suitable as a pharmaceutical substance.

10

In order to use the magnesium salt of omeprazole, in this specification denoted magnesium omeprazole, in full manufacturing scale in preparing pharmaceutical formulations primarily for oral administration, such as tablets, it is necessary that said magnesium omeprazole possesses a combination of properties which makes such full scale manufacturing feasible.

15

The combination of physical properties of the novel magnesium omeprazole product described in WO95/01977 with respect to the degree of crystallinity, particle diameter, density, hygroscopicity, low water content and low content of other solvents is favorable and permits the manufacture of magnesium omeprazole in a form which is advantageous for the manufacture of the new pharmaceutical formulations.

20

25

The novel form of magnesium omeprazole can be formulated into different dosage forms for oral and rectal administration. Examples of such formulations are tablets, granules, pellets, capsules, suppositories and suspensions.

30

Description of the invention

One object of the present invention is to provide a pharmaceutical formulation of magnesium omeprazole.

5

Another object of the present invention is to provide a process for full scale production of pharmaceutical formulations of omeprazole, especially an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability even against discoloration.

10

Yet another object of the invention is to provide an environmental friendly completely water-based process for the manufacture of pharmaceutical formulations of omeprazole.

15

A further object of the present invention is to provide a dosage form comprising omeprazole which is suitable for press-through blister packages and which also has an improved patient acceptance.

20

The new dosage form is characterized in the following way. Core material in the form of pellets, granules, beads or tablets containing the novel form of a magnesium salt of omeprazole and on said core material one or more enteric coating layers.

25

The process of forming the enteric coated dosage form is preferably water-based. Also the enteric coating process step can be carried out using a water-based process which is desirable both for the working environment inside the pharmaceutical plant and for global environmental reasons.

It has been found that a magnesium omeprazole having a degree of crystallinity which is higher than 70% is advantageous in the manufacture of pharmaceutical formulations of omeprazole according to the present invention.

5

Detailed description of the invention

The new pharmaceutical formulation is defined in claims 1-9, a process for the manufacture of the pharmaceutical formulation according to the present invention is defined in claims 10-11, the use of the formulation in medicine is defined in claims 12-18 and a press-through blister package is stated in claim 19.

Magnesium omeprazole

15 A magnesium omeprazole advantageous for the manufacturing of the claimed formulation is described in WO95/01977 hereby incorporated in a whole by reference. Said magnesium omeprazole has a degree of crystallinity of not less than 70%, preferably higher than 75% as determined by X-ray powder diffraction

20 Pharmaceutical formulations containing the magnesium omeprazole are manufactured as described herein below.

Core material

25 The novel magnesium salt of omeprazole, herein referred to as magnesium omeprazole, is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives,
30 can be used. The core may also contain an alkaline pharmaceutically acceptable

substance (or substances). The optionally added alkaline substance(s) is not essential for the invention. However, it may further improve the chemical stability of the formulations. Such pharmaceutically acceptable substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

The powder mixture is then formulated into pellets, granules, beads or tablets by pharmaceutical procedures. The pellets, granules, beads or tablets are used as core material for further processing.

Enteric coating layer

The enteric coating layer is applied in one or more layers onto the formulated core material by coating procedures in suitable equipments such as pan coating, coating granulator or fluidized bed apparatus using solutions of polymers in water, or by using latex suspensions of said polymers or optionally using polymer solutions in suitable organic solvents. As enteric coating polymers can be used one or more of the following, for example solutions or dispersions of acrylates (methacrylic acid/methacrylic acid methylester copolymer), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac or other suitable enteric coating polymer(s). Preferably water-based polymer dispersions such as for example compounds known

under the trade names Aquateric® (FMC Corporation) Eudragit® (Röhm Pharma), Aqoat™ (Shin-Etsu Chemical), Opadry™ (Colorcon) or similar compounds are used to obtain enteric coatings. The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer for example cetanol, triacetin, citric acid esters such as, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate, polyethylene glycol (PEG) or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-50 % of the enteric coating polymer(s). Additives such as talc, colorants and pigments may also be included into the enteric coating layer or sprayed onto the enteric coated material as an overcoat.

The thickness of the enteric coating may vary widely without influencing the release rate of omeprazole. To protect the acid susceptible omeprazole compound and to obtain an acceptable acid resistance, the enteric coating constitutes at least an amount of 1.0 % by weight of the core weight, preferably at least 3.0 % and more preferably more than 8.0 %. The upper amount of the applied enteric coating is normally only limited by processing conditions. This possibility to increase the thickness of the enteric coating without deleterious influence on the release rate of omeprazole is especially desirable in large scale processes. The enteric coating layer(s) may be applied on the pre-processed formulation without exactly controlling the thickness of the applied coating layer(s).

Thus, the formulation according to the invention consists of core material containing magnesium omeprazole. The core material is coated with enteric coating(s) rendering the dosage form insoluble in acid media, but disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, beads or granules, these pellets, beads or granules are dispensed in hard gelatin capsules or sachets. The final dosage form may further be coated with an additional layer containing pigment(s) and/or colourant(s). It is essential for the long term stability during storage that the water content of the final dosage form containing magnesium omeprazole (enteric coated tablets, capsules, granules, beads or pellets) is kept low.

Process

A process for the manufacture of a dosage form according to the present invention represents a further aspect of the invention. After the forming of the core material, said material is coated with enteric coating layer(s). The coating(s) are carried out as described above. Further another aspect of the invention is that the pharmaceutical processes can be completely water-based.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

The invention is illustrated in detail by the following examples. Examples 1-2 disclose compositions of different enteric coated tablets containing magnesium omeprazole. Said examples also show the result of a gastric acid resistance test in vitro. Example 3 discloses an enteric coated pellet formulation. Said example also shows the result of a gastric acid resistance test in vitro.

EXAMPLESExample 1

5 Tablet formulation containing magnesium omeprazole being produced as described in WO95/01977.

	Amount omeprazole	10
	Ingredient	(mg/tabl)
10	<u>Tablet core</u>	
	Magnesium omeprazole	11.2
	Mannitol	68.7
	Microcrystalline cellulose	25.0
	Sodium starch glycolate	6.0
15	Hydroxypropyl methylcellulose	6.0
	Talc	5.0
	Sodium stearyl fumarate	2.5
	Water purified	50.0
20	<u>Enteric coating layer</u>	
	Methacrylic acid copolymer	9.1
	Polyethylene glycol	1.0
	Titanium dioxide	0.82
	Colour iron oxide, red-brown	0.04
25	Colour iron oxide, yellow	0.02
	Water purified	45.0
	<u>Polish</u>	
	Paraffin powder	0.05
30		

Tablets with the composition described above have been manufactured in a laboratory scale of about 20 000 tablets.

Description of manufacturing

- 5 Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are enteric coated with a methacrylic acid copolymer film.
- 10 Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of acid-resistance

- Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.
- 15

20	Tablet	Acid resistance
	Strength	
	(mg)	(%)
	10	101 (98 - 103)

25 Example 2

Tablet formulation containing magnesium omeprazole being produced as described in WO95/01977.

30	Amount omeprazole	40
	Ingredient	(mg/tabl.)

Table core

	Magnesium omeprazole	45.0
	Mannitol	34.9
5	Microcrystalline cellulose	25.0
	Sodium starch glycolate	6.0
	Hydroxypropyl methylcellulose	6.0
	Talc	5.0
	Sodium stearyl fumarate	2.5
10	Water purified	50.0

Enteric coating layer

	Metacrylic acid copolymer	9.1
	Polyethylene glycol	1.0
15	Titanium dioxide	0.51
	Colour iron oxide red-brown	0.43
	Water purified	45.0

Polish

20	Paraffin	0.05
----	----------	------

Description of manufacturing

Magnesium omeprazole, mannitol, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate are dry-mixed, moistened with water and wet mixed. The wet mass is dried and milled and finally mixed with anti-adherent and lubricant substances. The milled granulate is compressed to tablets with a diameter of 7 mm. The tablets are enteric coated with a methacrylic acid copolymer film. Water used in the manufacture of the tablets is removed during subsequent processing.

Investigation of acid-resistance

Six individual tablets were exposed to artificial gastric fluid without enzymes, pH 1.2. After six hours the tablets were removed, washed and analysed for omeprazole content using HPLC. The amount of omeprazole is taken as acid resistance.

5

Tablet Strength (mg)	Acid resistance (%)
<hr/>	
10 40	95 (92-101)

Example 3

Enteric coated pellet formulation containing magnesium omeprazole being produced as described in WO95/01977.

15

Pellet Core

Magnesium omeprazole	1.5 kg
Non-pareil pellets	1.5 kg
20 Hydroxypropyl methylcellulose	0.23 kg
Water purified	4.0 kg

Enteric-coating layer

Uncoated pellets	500 g
25 Methacrylic acid copolymer	300 g
Triethyl citrate	90 g
Mono- and diglycerides (NF)	15 g
Polysorbate 80	1.5 g
Water purified	1290 g

30

Description of manufacturing.

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder. The prepared pellets were enteric-coated in a fluid
5 bed apparatus.

Investigation of acid resistance.

Pellets were added to gastric fluid USP (without enzyme), 37°C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the
10 formulation was determined.

		Acid resistance (n=6)		
Pellets		%		
<u>omeprazole</u>		<hr/>		
15	20 mg	94	(93	- 95)

CLAIMS

1. An oral enteric coated formulation containing a core material of an active substance coated with one or more enteric coating layers **characterized in** that the
5 core material as active substance contains a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction and on the core material enteric coating layer(s), whereby the thickness of the enteric coating does not essentially influence the release of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.
10
2. A formulation according to claim 1, wherein the formulation is a tablet formulation.
3. A formulation according to claim 1, wherein the formulation is a pellet
15 formulation.
4. A formulation according to claim 1, wherein the enteric coating comprising an enteric coating material, optionally containing one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.
20
5. A formulation according to claim 4, wherein the enteric coating comprises water-based polymer solutions or dispersions of acrylates, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate and/or cellulose acetate
25 phthalate.
6. A formulation according to claim 1, wherein the enteric coating constitutes from 1.0 % by weight of the weight of the core material.
- 30 7. A formulation according to claim 6, wherein the enteric coating constitutes at least 3.0 % by weight of the weight of the core material.

8. A formulation according to claim 6, wherein the enteric coating constitutes at least 8.0 % by weight of the weight of the core material.

9. A formulation according to claim 1, wherein one of the coating layers is an overcoat applied on the enteric coated formulation, which overcoat optionally comprises one or more pharmaceutically acceptable plasticizers, dispersants, colorants and pigments.

10. A process for the manufacture of a formulation according to claim 1 in which core material containing magnesium omeprazole is coated with one or more enteric coating layer(s), having a thickness which does not essentially influence the release rate of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.

11. A process according to claim 10 in which the enteric coated formulation is further coated with an overcoat.

12. An oral enteric coated formulation according to any of claims 1 to 9 for use in therapy.

13. An oral enteric coated formulation according to any of claims 1 to 9 for use in inhibiting gastric acid secretion in mammals and man.

14. An oral enteric coated formulation according to any of claims 1 to 9 for use in the treatment of gastric acid related diseases in mammals and man.

15. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals and man.

16. The use of an oral enteric coated formulation according to any of claims 1 to 9 in the manufacture of a medicament for treatment of gastric acid related diseases in mammals and man.

5 17. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

10 18. A method for the treatment of gastric acid related diseases in mammals and man by administering to a host in need thereof a therapeutically effective dose of an enteric coated formulation according to any of claims 1 to 9.

15 19. A press-through blister package comprising a formulation according to any of claims 1-9.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00816

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/24, A61K 9/52, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, MEDLINE, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9501783 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95) --	1-16,19
P,A	WO 9501977 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95) --	1-16,19
A	EP 0342522 A1 (EISAI CO., LTD.), 23 November 1989 (23.11.89) --	1-16,19
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) -- -----	1-16,19

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

30 October 1995

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/00816

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 95/00816

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO-A1-	9501783	19/01/95	NONE		
WO-A1-	9501977	19/01/95	NONE		
EP-A1-	0342522	23/11/89	SE-T3-	0342522	
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			SU-A-	1820837	07/06/93
			US-A-	4786505	22/11/88



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/24, 9/52, 31/44	A1	(11) International Publication Number: WO 96/01622 (43) International Publication Date: 25 January 1996 (25.01.96)
(21) International Application Number: PCT/SE95/00816 (22) International Filing Date: 3 July 1995 (03.07.95) (30) Priority Data: PCT/SE94/00679 8 July 1994 (08.07.94) WO <i>(34) Countries for which the regional or international application was filed:</i> SE et al. (60) Parent Application or Grant (63) Related by Continuation US 08/313,208 (CIP) Filed on 8 July 1994 (08.07.94) (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BENGTTSSON, Siv, Inga [SE/SE]; Klintens väg 13, S-414 76 Göteborg (SE). LÖVGREN, Kurt, Ingmar [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: NEW ORAL PHARMACEUTICAL FORMULATION CONTAINING MAGNESIUM SALT OF OMEPRAZOLE (57) Abstract <p>A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole coated with one or more enteric coating layers, a method for the manufacture of such a formulation, the use of such a formulation in medicine and a blister package containing the new formulation.</p>		

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